# THE AMERICAN JOURNAL OF PSYCHIATRY

Volume 147, Number 8 August 1990

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Utilization Management of Mental Health Services by Private Third Parties

By Gary L. Tischler

The Relation of Ulcerative Colitis to Psychiatric Factors: A Review of Findings and Methods

By Carol S. North, Ray E. Clouse, Edward L. Spitznagel, et al.

Official Journal of the American Psychiatric Association

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# Her anxiolytic is working— but she's alert, functioning, and at no risk of a benzodiazepine withdrawal syndrome when therapy ends.


That's

# Efficacy!

## BuSpar® (buspirone HCl)

**References: 1.** Rickels K, et al. Buspirone and diazepam in anxiety: A controlled study. *J Clin Psychiatry* 1982;43(12, Sec 2):81-86. **2.** Newton RE, et al: A review of the side effect profile of buspirone. *Am J Med* 1986;80(suppl 3B):17-21. **3.** Lucki I, et al: Differential effects of the anxiolytic drugs, diazepam and buspirone, on memory function. *Br J Clin Pharmacol* 1987;23:207-211. **4.** Lader M: Assessing the potential for buspirone dependence or abuse and effects of its withdrawal. *Am J Med* 1987;82(suppl 5A):20-26.

**Contraindications:** Hypersensitivity to buspirone hydrochloride.

**Warnings: The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard.** Since blood pressure has become elevated when BuSpar was administered concomitantly with an MAOI, such concomitant use is not recommended. BuSpar should not be employed in lieu of appropriate antipsychotic treatment.

**Precautions:** ***General***—*Interference with cognitive and motor performance:* Although buspirone is less sedating than other anxiolytics and does not produce significant functional impairment, its CNS effects in a given patient may not be predictable; therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone does not affect them adversely. Although buspirone has not been shown to increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use with alcohol.

*Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug dependent patients:* Because buspirone will not block the withdrawal syndrome often seen with cessation of therapy with benzodiazepines and other common sedative/hypnotic drugs, before starting buspirone withdraw patients gradually from their prior treatment, especially those who used a CNS depressant chronically. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its elimination half-life. The withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

*Possible concerns related to buspirone's binding to dopamine receptors:* Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (eg, dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported; the syndrome may be due to increased central noradrenergic activity or may be attributable to dopaminergic effects (ie, represent akathisia).

***Information for Patients***—Patients should be instructed to inform their physician about any medications, prescription or nonprescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone; to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone; to inform their physician if they are breast feeding; and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.

***Drug Interactions***—Concomitant use with other CNS active drugs should be approached with caution (see **Warnings**). Concomitant use with trazodone may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. Concomitant administration of BuSpar and haloperidol resulted in increased serum haloperidol concentrations in normal volunteers. The clinical significance is not clear. Buspirone does not displace tightly bound drugs like phenytoin, propranolol, and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin. However, there was one report of prolonged prothrombin time when buspirone was given to a patient also treated with warfarin, phenytoin, phenobarbital, digoxin, and Synthroid.

***Carcinogenesis, Mutagenesis, Impairment of Fertility***—No evidence of carcinogenic potential was observed in rats or mice; buspirone did not induce point mutations, nor was DNA damage observed; chromosomal aberrations or abnormalities did not occur.

***Pregnancy: Teratogenic Effects***—Pregnancy Category B: Should be used during pregnancy only if clearly needed.

***Nursing Mothers***—Administration to nursing women should be avoided if clinically possible.

***Pediatric Use***—The safety and effectiveness have not been determined in individuals below 18 years of age.

***Use in the Elderly***—No unusual, adverse, age-related phenomena have been identified in elderly patients receiving a total, modal daily dose of 15 mg.

***Use in Patients with Impaired Hepatic or Renal Function***—Since buspirone is metabolized by the liver and excreted by the kidneys, it is not recommended in severe hepatic or renal impairment.

**Adverse Reactions (See also Precautions):** ***Commonly Observed***—The more commonly observed untoward events, not seen at an equivalent incidence in placebo-treated patients, include dizziness, nausea, headache, nervousness, lightheadedness, and excitement.

***Associated with Discontinuation of Treatment***—The more common events causing discontinuation in

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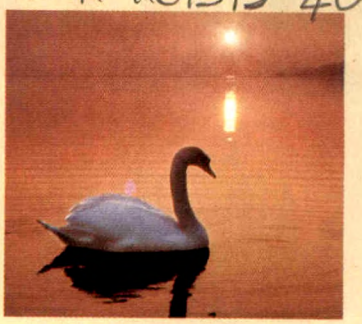
*Effective choice for anxiety*

# BuSpar®
Tablets
5 mg and 10 mg

# (buspirone HCl)

*for a different kind of calm*





BuSpar cuts the link between efficacy and CNS-depressant effects

BuSpar relieves anxiety[1] and returns your patient to normal activity

- . . . with no more drowsiness (10%) than induced by placebo (9%)[2]
- . . . without significant cognitive[3] or functional impairment*
- . . . without a benzodiazepine withdrawal syndrome on discontinuation[4]

## *Well tolerated*

The more commonly observed untoward events associated with the use of BuSpar not seen at an equivalent incidence among placebo-treated patients include dizziness (12%), nausea (8%), headache (6%), nervousness (5%), lightheadedness (3%), and excitement (2%).

*Because the effects of BuSpar in any individual patient may not be predictable, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that BuSpar treatment does not affect them adversely.



cluded: central nervous system disturbances (3.4%), primarily dizziness, insomnia, nervousness, drowsiness, lightheaded feeling; gastrointestinal disturbances (1.2%), primarily nausea; miscellaneous disturbances (1.1%), primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary.

***Incidence in Controlled Clinical Trials***—Adverse events reported by 1% or more of 477 patients who received buspirone in four-week, controlled trials: *Cardiovascular:* Tachycardia/palpitations 1%. *CNS:* Dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, lightheadedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2%. *EENT:* Blurred vision 2%. *Gastrointestinal:* Nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1%. *Musculoskeletal:* Musculoskeletal aches/pains 1%. *Neurological:* Numbness 2%, paresthesia 1%, incoordination 1%, tremor 1%. *Skin:* Skin rash 1%. *Miscellaneous:* Headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%.

***Other Events Observed During the Entire Premarketing Evaluation***—The relative frequency of all other undesirable events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under well-controlled, open, and uncontrolled conditions is defined as follows: Frequent are those occurring in at least 1/100 patients; infrequent are those occurring in 1/100 to 1/1000 patients; and rare are those occurring in less than 1/1000 patients. *Cardiovascular*—frequent: non-specific chest pain; infrequent: syncope, hypotension, hypertension; rare: cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, bradycardia. *Central Nervous System*—frequent: dream disturbances; infrequent: depersonalization, dysphoria, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, dissociative reaction, hallucinations, suicidal ideation, seizures; rare: feelings of claustrophobia, cold intolerance, stupor, slurred speech, psychosis. *EENT*—frequent: tinnitus, sore throat, nasal congestion; infrequent: redness and itching of the eyes, altered taste, altered smell, conjunctivitis; rare: inner ear abnormality, eye pain, photophobia, pressure on eyes. *Endocrine*—rare: galactorrhea, thyroid abnormality. *Gastrointestinal*—infrequent: flatulence, anorexia, increased appetite, salivation, irritable colon, rectal bleeding; rare: burning of the tongue. *Genitourinary*—infrequent: urinary frequency, urinary hesitancy, menstrual irregularity and spotting, dysuria; rare: amenorrhea, pelvic inflammatory disease, enuresis, nocturia. *Musculoskeletal*—infrequent: muscle cramps, muscle spasms, rigid/stiff muscles, arthralgias. *Neurological*—infrequent: involuntary movements, slowed reaction time; rare: muscle weakness. *Respiratory*—infrequent: hyperventilation, shortness of breath, chest congestion; rare: epistaxis. *Sexual Function*—infrequent: decreased or increased libido; rare: delayed ejaculation, impotence. *Skin*—infrequent: edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, blisters; rare: acne, thinning of nails. *Clinical Laboratory*—infrequent: increases in hepatic aminotransferases (SGOT, SGPT); rare: eosinophilia, leukopenia, thrombocytopenia. *Miscellaneous*—infrequent: weight gain, fever, roaring sensation in the head, weight loss, malaise; rare: alcohol abuse, bleeding disturbance, loss of voice, hiccoughs.

***Postintroduction Clinical Experience***—Rare occurrences of allergic reactions, cogwheel rigidity, dystonic reactions, ecchymosis, emotional lability, tunnel vision, and urinary retention have been reported. Because of the uncontrolled nature of these spontaneous reports, a causal relationship to BuSpar has not been determined.

**Drug Abuse and Dependence:** ***Controlled Substance Class***—Not a controlled substance.

***Physical and Psychological Dependence***—Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (eg, development of tolerance, incrementation of dose, drug-seeking behavior).

**Overdosage:** ***Signs and Symptoms***—At doses approaching 375 mg/day the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. No deaths have been reported in humans either with deliberate or accidental overdosage.

***Recommended Overdose Treatment***—General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined.

*For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceuticals Representative.*

U.S. Patent Nos. 3,717,634 and 4,182,763

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# THE AMERICAN JOURNAL OF PSYCHIATRY



*The American Journal of Psychiatry*, ISSN 0002-953X, is published monthly by the American Psychiatric Association, 1400 K Street, N.W., Washington, DC 20005. Subscriptions: U.S. $56.00 (student $28.00) per year, Canada and foreign $86.00 (student $43.00); single issues: U.S. $7.00, Canada and foreign $10.00.

Business communications, changes of address, and questions about subscriptions from APA members should be directed to the Division of Member Services: (202) 682-6090. Communications from nonmember subscribers should be directed to the Circulation Department: (202) 682-6158. Authors who wish to contact the *Journal* editorial office should call (202) 682-6020 or FAX (202) 682-6016.

Business Management: Nancy Frey, Director, Periodicals Services; Laura G. Abedi, Advertising Production Manager: (202) 682-6154; Beth Prester, Director, Circulation; Karen Loper, Promotion Manager; Jackie Coleman, Fulfillment Manager.

Advertising Sales: Raymond J. Purkis, Director, 2444 Morris Avenue, Union, NJ 07083; (201) 964-3100.

Type set by Byrd Data Imaging Group, Richmond, VA. Printed by The William Byrd Press, Inc., Richmond, VA.

Second-class postage paid at Washington, DC, and additional mailing offices. POSTMASTER: Send address changes to *The American Journal of Psychiatry*, Circulation Department, American Psychiatric Association, 1400 K St., N.W., Washington, DC 20005.

Indexed in *Abstracts for Social Workers, Biological Abstracts, Chemical Abstracts, Chicago Psychoanalytic Literature Index, Cumulative Index to Nursing Literature, Excerpta Medica, Hospital Literature Index, Index Medicus, International Nursing Index, Nutrition Abstracts, Psychological Abstracts, Science Citation Index,* and *Social Sciences Index.*

THE AMERICAN JOURNAL OF PSYCHIATRY

Volume 147, Number 8 August 1990


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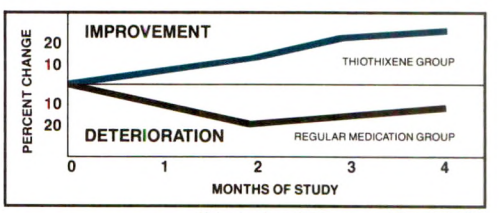
# "IT FEELS GOOD TO FEEL USEFUL AGAIN"

For the chronic schizophrenic patient, Navane can mean more competent work performance,[1,2] and a smoother path towards social recovery. Navane may help improve the ability to concentrate, and promote a better attitude toward work and co-workers.[1-3]

Anticholinergic[4] and cardiovascular[5,6] side effects in patients treated with Navane are reported infrequently. Should extrapyramidal symptoms occur, they usually can be controlled.

**27% rise in work output compared to baseline shown in patients switched to Navane[2,3]**




(Adapted from DiMascio and Demirgian[2,3])

Forty-two psychotic male and female patients under age 55 were entered in this study on a nonblind basis, and randomly assigned to their regular medication or switched to thiothixene. Patients were evaluated at baseline and on a daily basis, and periodically rated on the Global Improvement and Brief Psychiatric Rating Scales.

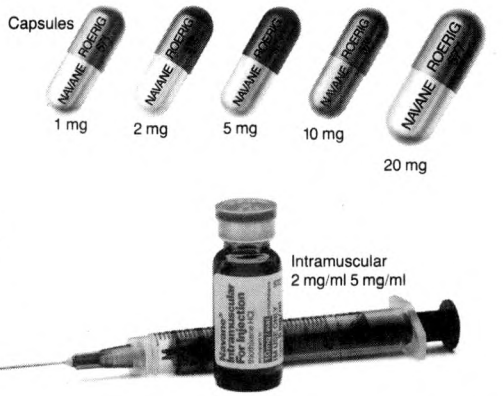
**In schizophrenia,**

# Navane® (thiothixene) (thiothixene HCl)

Please see brief summary of NAVANE® (thiothixene/thiothixene HCl) prescribing information on adjacent page.

# Navane®
## (thiothixene) (thiothixene HCl)

## *It feels good to feel useful again*




Concentrate
5 mg/ml

**References:** 1. Bressler B, Friedel RO: A comparison between chlorpromazine and thiothixene in a Veterans Administration hospital population. *Psychosomatics* 1971;12:275-277. 2. DiMascio A, Demirgian E: Study of the activating properties of thiothixene. *Psychosomatics* 1972;13:105-108. 3. DiMascio A, Demirgian E: Job training in the rehabilitation of the chronic schizophrenic. Presented as a Scientific Exhibit at The American Psychiatric Association. Washington, DC, May 3-6, 1971. 4. Goldstein B, Weiner D, Banas F: Clinical evaluation of thiothixene in chronic ambulatory schizophrenic patients, in Lehmann HE, Ban TA (eds): *The Thioxanthenes: Modern Problems of Pharmacopsychiatry.* Basel, Switzerland, S. Karger, 1969, vol 2, pp 45-52. 5. Dillenkoffer RL, Gallant DM, George RB, et al: Electrocardiographic evaluation of schizophrenic patients: A double-blind comparison. Presented as a Scientific Exhibit at The 125th Annual Meeting of the American Psychiatric Association, Dallas, May 1-4, 1972. 6. Data available on request from Roerig.

**BRIEF SUMMARY OF PRESCRIBING INFORMATION**
**Navane® (thiothixene) Capsules: 1 mg, 2 mg, 5 mg, 10 mg, 20 mg**
**(thiothixene hydrochloride) Concentrate: 5 mg/ml, Intramuscular: 2 mg/ml, 5 mg/ml**
**Indications:** Navane is effective in the management of manifestations of psychotic disorders. Navane has not been evaluated in the management of behavioral complications in patients with mental retardation.
**Contraindications:** Contraindicated in patients with circulatory collapse, comatose states, central nervous system depression due to any cause, and blood dyscrasias. Contraindicated in individuals who have shown hypersensitivity to the drug. It is not known whether there is a cross-sensitivity between the thioxanthenes and the phenothiazine derivatives, but the possibility should be considered.
**Warnings:** *Tardive Dyskinesia*—Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to neuroleptic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are *not* available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to Information for Patients in the Precautions section, and to the Adverse Reactions section.)

*Neuroleptic Malignant Syndrome (NMS)*—A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

*Usage in Pregnancy*—Safe use of Navane during pregnancy has not been established. Therefore, this drug should be given to pregnant patients only when, in the judgment of the physician, the expected benefits from the treatment exceed the possible risks to mother and fetus. Animal reproduction studies and clinical experience to date have not demonstrated any teratogenic effects.

In the animal reproduction studies with Navane, there was some decrease in conception rate and litter size, and an increase in resorption rate in rats and rabbits, changes which have been similarly reported with other psychotropic agents. After repeated oral administration of Navane to rats (5 to 15 mg/kg/day), rabbits (3 to 50 mg/kg/day), and monkeys (1 to 3 mg/kg/day) before and during gestation, no teratogenic effects were seen. (See Precautions.)

*Usage in Children*—The use of Navane in children under 12 years of age is not recommended because safety and efficacy in the pediatric age group have not been established.

As is true with many CNS drugs, Navane may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, especially during the first few days of therapy. Therefore, the patient should be cautioned accordingly.

As in the case of other CNS-acting drugs, patients receiving Navane should be cautioned about the possible additive effects (which may include hypotension) with CNS depressants and with alcohol.
**Precautions:** An antiemetic effect was observed in animal studies with Navane; since this effect may also occur in man, it is possible that Navane may mask signs of overdosage of toxic drugs and may obscure conditions such as intestinal obstruction and brain tumor.

In consideration of the known capability of Navane and certain other psychotropic drugs to precipitate convulsions, extreme caution should be used in patients with a history of convulsive disorders or those in a state of alcohol withdrawal since it may lower the convulsive threshold. Although Navane potentiates the actions of the barbiturates, the dosage of the anticonvulsant therapy should not be reduced when Navane is administered concurrently.

Caution as well as careful adjustment of the dosage is indicated when Navane is used in conjunction with other CNS depressants other than anticonvulsant drugs.

Though exhibiting rather weak anticholinergic properties, Navane should be used with caution in patients who are known or suspected to have glaucoma, or who might be exposed to extreme heat, or who are receiving atropine or related drugs.

Use with caution in patients with cardiovascular disease.

Also, careful observation should be made for pigmentary retinopathy, and lenticular pigmentation (fine lenticular pigmentation has been noted in a small number of patients treated with Navane for prolonged periods). Blood dyscrasias (agranulocytosis, pancytopenia, thrombocytopenic purpura), and liver damage (jaundice, biliary stasis) have been reported with related drugs.

Undue exposure to sunlight should be avoided. Photosensitive reactions have been reported in patients on Navane (thiothixene).

*Intramuscular Administration*—As with all intramuscular preparations, Navane Intramuscular should be injected well within the body of a relatively large muscle. The preferred sites are the upper outer quadrant of the buttock (i.e. gluteus maximus) and the mid-lateral thigh.

The deltoid area should be used only if well developed, such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made into the lower and mid-thirds of the upper arm. As with all intramuscular injections, aspiration is necessary to help avoid inadvertent injection into a blood vessel.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

*Information for Patients*—Given the likelihood that some patients exposed chronically to neuroleptics will develop tardive dyskinesia, it is advised that all patients in whom chronic use is contemplated be given, if possible, full information about this risk. The decision to inform patients and/or their guardians must obviously take into account the clinical circumstances and the competency of the patient to understand the information provided.
**Adverse Reactions:** *Note:* Not all of the following adverse reactions have been reported with Navane (thiothixene). However, since Navane has certain chemical and pharmacologic similarities to the phenothiazines, all of the known side effects and toxicity associated with phenothiazine therapy should be borne in mind when Navane is used.

Cardiovascular effects: Tachycardia, hypotension, lightheadedness, and syncope. In the event hypotension occurs, epinephrine should not be used as a pressor agent since a paradoxical further lowering of blood pressure may result. Nonspecific EKG changes have been observed in some patients receiving Navane (thiothixene). These changes are usually reversible and frequently disappear on continued Navane therapy. The incidence of these changes is lower than that observed with some phenothiazines. The clinical significance of these changes is not known.

CNS effects: Drowsiness, usually mild, may occur although it usually subsides with continuation of Navane therapy. The incidence of sedation appears similar to that of the piperazine group of phenothiazines, but less than that of certain aliphatic phenothiazines. Restlessness, agitation and insomnia have been noted with Navane. Seizures and paradoxical exacerbation of psychotic symptoms have occurred with Navane infrequently.

Hyperreflexia has been reported in infants delivered from mothers having received structurally related drugs.

In addition, phenothiazine derivatives have been associated with cerebral edema and cerebrospinal fluid abnormalities.

Extrapyramidal symptoms, such as pseudo-parkinsonism, akathisia, and dystonia have been reported. Management of these extrapyramidal symptoms depends upon the type and severity. Rapid relief of acute symptoms may require the use of an injectable antiparkinson agent. More slowly emerging symptoms may be managed by reducing the dosage of Navane and/or administering an oral antiparkinson agent.

Persistent Tardive Dyskinesia: As with all antipsychotic agents tardive dyskinesia may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities.

Since early detection of tardive dyskinesia is important, patients should be monitored on an ongoing basis. It has been reported that fine vermicular movement of the tongue may be an early sign of the syndrome. If this or any other presentation of the syndrome is observed, the clinician should consider possible discontinuation of neuroleptic medication. (See Warnings section.)

Hepatic Effects: Elevations of serum transaminase and alkaline phosphatase, usually transient, have been infrequently observed in some patients. No clinically confirmed cases of jaundice attributable to Navane have been reported.

Hematologic Effects: As is true with certain other psychotropic drugs, leukopenia and leukocytosis, which are usually transient, can occur occasionally with Navane. Other antipsychotic drugs have been associated with agranulocytosis, eosinophilia, hemolytic anemia, thrombocytopenia and pancytopenia.

Allergic Reactions: Rash, pruritus, urticaria, photosensitivity and rare cases of anaphylaxis have been reported with Navane. Undue exposure to sunlight should be avoided. Although not experienced with Navane, exfoliative dermatitis and contact dermatitis (in nursing personnel) have been reported with certain phenothiazines.

Endocrine Disorders: Lactation, moderate breast enlargement and amenorrhea have occurred in a small percentage of females receiving Navane. If persistent, this may necessitate a reduction in dosage or the discontinuation of therapy. Phenothiazines have been associated with false positive pregnancy tests, gynecomastia, hypoglycemia, hyperglycemia, and glycosuria.

Autonomic Effects: Dry mouth, blurred vision, nasal congestion, constipation, increased sweating, increased salivation, and impotence have occurred infrequently with Navane therapy. Phenothiazines have been associated with miosis, mydriasis, and adynamic ileus.

Other Adverse Reactions: Hyperpyrexia, anorexia, nausea, vomiting, diarrhea, increase in appetite and weight, weakness or fatigue, polydipsia and peripheral edema.

Although not reported with Navane, evidence indicates there is a relationship between phenothiazine therapy and the occurrence of a systemic lupus erythematosus-like syndrome.

*Neuroleptic Malignant Syndrome (NMS): Please refer to the text regarding NMS in the WARNINGS section.*

NOTE: Sudden deaths have occasionally been reported in patients who have received certain phenothiazine derivatives. In some cases the cause of death was apparently cardiac arrest or asphyxia due to failure of the cough reflex. In others, the cause could not be determined nor could it be established that death was due to phenothiazine administration.
**Dosage:** Dosage of Navane should be individually adjusted depending on the chronicity and severity of the condition. See full prescribing information.
**Overdosage:** For information on signs and symptoms, and treatment of overdosage, see full prescribing information.

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A logical choice among antidepressants

**A 25-year history** of proven clinical usefulness with unsurpassed **flexibility of dosage** provided by 6 tablet strengths, **color coded** to ensure exact identification. It also offers **dose equivalence** that permits prescribing one tablet of greater strength in place of multiple doses of lesser strengths, resulting in **increased patient compliance** and greater than **20% cost savings.**

**Ensure the maximum benefits of Norpramin by specifying "Dispense As Written."**

- A 25-year record of efficacy in relieving the **symptoms** of depression*
- Less anticholinergic activity than amitriptyline or doxepin*
- Usually no excessive daytime drowsiness (see Warnings)†

# Norpramin

(desipramine hydrochloride tablets USP)

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†Norpramin does not usually inhibit normal activity, although patients should be cautioned against driving or operating machinery if drowsiness occurs (see Warnings, Precautions, and Adverse Reactions).

8-1912 (NR081) February, 1989 Printed in U.S.A.

# Norpramin®

10, 25, 50, 75, 100, 150 mg

# (desipramine hydrochloride tablets USP)

## Norpramin®

(desipramine hydrochloride tablets USP)

**BRIEF SUMMARY**

CAUTION: Federal law prohibits dispensing without prescription.

**INACTIVE INGREDIENTS**

The following inactive ingredients are contained in all dosage strengths: acacia, calcium carbonate, corn starch, D&C Red No. 30 and D&C Yellow No. 10 (except 10 mg and 150 mg), FD&C Blue No. 1, FD&C Red No. 3, FD&C Yellow No. 6, hydrogenated soy oil, iron oxide, light mineral oil, magnesium stearate, mannitol, polyethylene glycol 8000, pregelatinized corn starch, sodium benzoate (except 150 mg), sucrose, talc, titanium dioxide, and other ingredients.

**CLINICAL PHARMACOLOGY**

*Metabolism*

The rate of metabolism of tricyclic antidepressants varies widely from individual to individual, chiefly on a genetically determined basis. In general, the elderly metabolize tricyclic antidepressants more slowly than do younger adults.

Certain drugs, particularly the psychostimulants and the phenothiazines, increase plasma levels of concomitantly administered tricyclic antidepressants through competition for the same metabolic enzyme systems. Other substances, particularly barbiturates and alcohol, induce liver enzyme activity and thereby reduce tricyclic antidepressant plasma levels. Similar effects have been reported with tobacco smoke.

Additional information on metabolism appears in Full Prescribing Information.

**CONTRAINDICATIONS**

Desipramine hydrochloride should not be given in conjunction with, or within 2 weeks of, treatment with an MAO inhibitor drug; hyperpyretic crises, severe convulsions, and death have occurred in patients taking MAO inhibitors and tricyclic antidepressants. When Norpramin (desipramine hydrochloride) is substituted for an MAO inhibitor, at least 2 weeks should elapse between treatments. Norpramin should then be started cautiously and should be increased gradually.

The drug is contraindicated in the acute recovery period following myocardial infarction. It should not be used in those who have shown prior hypersensitivity to the drug. Cross sensitivity between this and other dibenzazepines is a possibility.

**WARNINGS**

1. Extreme caution should be used when this drug is given in the following situations:
   a. In patients with cardiovascular disease, because of the possibility of conduction defects, arrhythmias, tachycardias, strokes, and acute myocardial infarction.
   b. In patients with a history of urinary retention or glaucoma, because of the anticholinergic properties of the drug.
   c. In patients with thyroid disease or those taking thyroid medication, because of the possibility of cardiovascular toxicity, including arrhythmias.
   d. In patients with a history of seizure disorder, because this drug has been shown to lower the seizure threshold.
2. This drug is capable of blocking the antihypertensive effect of guanethidine and similarly acting compounds.
3. **USE IN PREGNANCY**
   Safe use of desipramine hydrochloride during pregnancy and lactation has not been established; therefore, if it is to be given to pregnant patients, nursing mothers, or women of childbearing potential, the possible benefits must be weighed against the possible hazards to mother and child. Animal reproductive studies have been inconclusive.
4. **USE IN CHILDREN**
   Norpramin (desipramine hydrochloride) is not recommended for use in children since safety and effectiveness in the pediatric age group have not been established. (See ADVERSE REACTIONS, Cardiovascular.)
5. The patient should be cautioned that this drug may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.
6. In patients who may use alcohol excessively, it should be borne in mind that the potentiation may increase the danger inherent in any suicide attempt or overdosage.

**PRECAUTIONS**

1. It is important that this drug be dispensed in the least possible quantities to depressed outpatients, since suicide has been accomplished with this class of drug. Ordinary prudence requires that children not have access to this drug or to potent drugs of any kind; if possible, this drug should be dispensed in containers with child-resistant safety closures. Storage of this drug in the home must be supervised responsibly.
2. If serious adverse effects occur, dosage should be reduced or treatment should be altered.
3. Norpramin (desipramine hydrochloride) therapy in patients with manic-depressive illness may induce a hypomanic state after the depressive phase terminates.
4. The drug may cause exacerbation of psychosis in schizophrenic patients.
5. Close supervision and careful adjustment of dosage are required when this drug is given concomitantly with anticholinergic or sympathomimetic drugs.
6. Patients should be warned that while taking this drug their response to alcoholic beverages may be exaggerated.
7. Clinical experience in the concurrent administration of ECT and antidepressant drugs is limited. Thus, if such treatment is essential, the possibility of increased risk relative to benefits should be considered.
8. If Norpramin (desipramine hydrochloride) is to be combined with other psychotropic agents such as tranquilizers or sedative/hypnotics, careful consideration should be given to the pharmacology of the agents employed since the sedative effects of Norpramin and benzodiazepines (e.g., chlordiazepoxide or diazepam) are additive. Both the sedative and anticholinergic effects of the major tranquilizers are also additive to those of Norpramin.
9. Concurrent administration of cimetidine and tricyclic antidepressants can produce clinically significant increases in the plasma levels of the tricyclic antidepressants. Conversely, decreases in plasma levels of the tricyclic antidepressants have been reported upon discontinuation of cimetidine which may result in the loss of the therapeutic efficacy of the tricyclic antidepressant.
10. This drug should be discontinued as soon as possible prior to elective surgery because of the possible cardiovascular effects. Hypertensive episodes have been observed during surgery in patients taking desipramine hydrochloride.
11. Both elevation and lowering of blood sugar levels have been reported.
12. Leukocyte and differential counts should be performed in any patient who develops fever and sore throat during therapy; the drug should be discontinued if there is evidence of pathologic neutrophil depression.

**ADVERSE REACTIONS**

Note: Included in the following listing are a few adverse reactions that have not been reported with this specific drug. However, the pharmacologic similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when Norpramin (desipramine hydrochloride) is given.

*Cardiovascular:* hypotension, hypertension, tachycardia, palpitation, arrhythmias, heart block, myocardial infarction, stroke. There has been a report of an "acute collapse" and "sudden death" in an eight-year old (18 kg) male, treated for two years for hyperactivity. (See WARNINGS, Use in Children.)

*Psychiatric:* confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia and nightmares; hypomania; exacerbation of psychosis.

*Neurologic:* numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures; alteration in EEG patterns; tinnitus.

*Anticholinergic:* dry mouth, and rarely associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis, increased intraocular pressure; constipation, paralytic ileus; urinary retention, delayed micturition, dilatation of urinary tract.

*Allergic:* skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight), edema (of face and tongue or general), drug fever, cross sensitivity with other tricyclic drugs.

*Hematologic:* bone marrow depressions including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

*Gastrointestinal:* anorexia, nausea and vomiting, epigastric distress, peculiar taste, abdominal cramps, diarrhea, stomatitis, black tongue.

*Endocrine:* gynecomastia in the male, breast enlargement and galactorrhea in the female; increased or decreased libido, impotence, painful ejaculation, testicular swelling; elevation or depression of blood sugar levels; syndrome of inappropriate antidiuretic hormone secretion (SIADH).

*Other:* jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration, flushing; urinary frequency, nocturia; parotid swelling; drowsiness, dizziness, weakness and fatigue, headache; alopecia.

*Withdrawal Symptoms:* Though not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

**OVERDOSAGE**

There is no specific antidote for desipramine, nor are there specific phenomena of diagnostic value characterizing poisoning by the drug.

Within an hour of ingestion the patient may become agitated or stuporous and then comatose. Hypotension, shock, and renal shutdown may ensue. Grand mal seizures, both early and late after ingestion, have been reported. Hyperactive reflexes, hyperpyrexia, muscle rigidity, vomiting, and ECG evidence of impaired conduction may occur. Serious disturbances of cardiac rate, rhythm, and output can occur. The precepts of early evacuation of the ingested material and subsequent support of respiration (airway and movement), circulation, and renal output apply.

The principles of management of coma and shock by means of the mechanical respirator, cardiac pacemaker, monitoring of central venous pressure, and regulation of fluid and acid-base balance are well known in most medical centers and are not further discussed here.

Because CNS involvement, respiratory depression, and cardiac arrhythmia can occur suddenly, hospitalization and close observation are generally advisable, even when the amount ingested is thought to be small or the initial degree of intoxication appears slight or moderate. Most patients with ECG abnormalities should have continuous cardiac monitoring for at least 72 hours and be closely observed until well after cardiac status has returned to normal; relapses may occur after apparent recovery.

The slow intravenous administration of physostigmine salicylate has been reported to reverse most of the anticholinergic cardiovascular and CNS effects of overdose with tricyclic antidepressants. In adults, 1 to 3 mg has been reported to be effective. In children, the dose should be started with 0.5 mg and repeated at 5-minute intervals to determine the minimum effective dose; no more than 2 mg should be given. Because of the short duration of action of physostigmine, the effective dose should be repeated at 30-minute to 60-minute intervals, as necessary. Rapid injection should be avoided to reduce the possibility of physostigmine-induced convulsions.

Other possible therapeutic considerations include:

(a) Dialysis: Desipramine is found in low concentration in the serum, even after a massive oral dose. In vitro experiments in which blood bank blood was used indicate that it is very poorly dialyzed. Because of indications that the drug is secreted in gastric juice, constant gastric lavage has been suggested.

(b) Pharmacologic treatment of shock: Since desipramine potentiates the action of such vasopressor agents as levarterenol and metaraminol, they should be used only with caution.

(c) Pharmacologic control of seizures: Intravenous barbiturates are the treatment of choice for the control of grand mal seizures. One may, alternatively, consider the parenteral use of diphenylhydantoin, which has less central depressant effect but also has an effect on heart rhythm that has not yet been fully defined.

(d) Pharmacologic control of cardiac function: Severe disturbances of cardiac rate, rhythm, and output are probably the initiating events in shock. Intravascular volume must be maintained by I.V. fluids. Digitalization should be carried out early in view of the fact that a positive inotropic effect can be achieved without increase in cardiac work. Many of the cardiodynamic effects of digitalis are the exact opposite of those of massive doses of desipramine (animal studies).

Product Information as of January, 1989 Y398D

MERRELL DOW PHARMACEUTICALS INC.
Cincinnati, Ohio 45215, U.S.A.

Merrell Dow

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*1400 K Street, N.W., Washington, D.C. 20005*

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# *Books Received*

**Too Good for Her Own Good: Breaking Free From the Burden of Female Responsibility**, by Claudia Bepko and Jo-Ann Krestan. New York, Harper & Row, 1990, 245 pp., $17.95.

**Community Care of the Chronically Mentally Ill: Proceedings of the Sixth Robert Lee Sunderland Seminar in Mental Health**, edited by Charles M. Bonjean, Marion Tolbert Coleman, and Ira Iscoe. Austin, Tex., Hogg Foundation for Mental Health, University of Texas, 1990, 280 pp., $7.25 (paper).

**Family Therapy for Adolescent Drug Abuse**, edited by Alfred M. Friedman and Samuel Granick. Lexington, Mass., Lexington Books (D.C. Heath and Co.), 1990, 427 pp., $44.95.

**Making Connections: The Relational Worlds of Adolescent Girls at Emma Willard School**, edited by Carol Gilligan, Nona P. Lyons, and Trudy J. Hanmer. Cambridge, Mass., Harvard University Press, 1990, 334 pp., $25.00; $10.95 (paper).

**Broadening the Base of Treatment for Alcohol Problems: Report of a Study by a Committee of the Institute of Medicine, Division of Mental Health and Behavioral Medicine.** Washington, D.C., National Academy Press, 1990, 609 pp., $45.00.

**Child Abuse: A Practical Guide for Those Who Help Others**, by E. Clay Jorgensen. New York, Continuum, 1990, 135 pp., $16.95.

**The Act of Creation** (1964), by Arthur Koestler. New York, Arkana (Penguin), 1990, 728 pp., $10.95 (paper).

**Handbook of Hospital Based Substance Abuse Treatment**, edited by William D. Lerner, M.D., and Marjorie A. Barr, M.S.W. Oxford, England, Pergamon Press, 1990, 209 pp., $44.50; $22.50 (paper).

**Mercy**, by David Lindsey. New York, Doubleday, 1990, 513 pp., $19.95.

**Treatment Choices for Alcoholism and Substance Abuse**, edited by Harvey B. Milkman, Ph.D., and Lloyd I. Sederer, M.D. Lexington, Mass., Lexington Books (D.C. Heath and Co.), 1990, 379 pp., $49.00.

**Annual Report to Congress, 1990**, by the Physician Payment Review Commission. Washington, D.C., Physician Payment Review Commission, 1990, 342 pp., no price listed (paper).

**When I Grow Up I Want to Be an Adult: Christ-Centered Recovery for Adult Children**, by Ron Ross. San Diego, Recovery Publications, 1990, 205 pp., $11.95 (paper).

**The Drunken Society: Alcohol Abuse and Alcoholism in the Soviet Union. A Comparative Study**, by Boris M. Segal. New York, Hippocrene Books, 1990, 606 pp., $40.00.

**Institutes and How to Survive Them: Mental Health Training and Consultation. Selected Papers by Robin Skynner**, edited by John R. Schlapobersky. New York, Routledge, 1990, 222 pp., $29.95.

**Too Scared to Cry: Psychic Trauma in Childhood**, by Lenore Terr, M.D. New York, Harper & Row, 1990, 365 pp., $21.95.

**Circle of Hope: Our Stories of AIDS, Addiction, and Recovery**, by Perry Tilleraas. Center City, Minn., Hazelden, 1990, 364 pp., no price listed (paper).

**White Bears and Other Unwanted Thoughts: Suppression, Obsession, and the Psychology of Mental Control** (1989), by Daniel W. Wegner. New York, Penguin Books, 1990, 198 pp., $7.95 (paper).

# Calendar

*For free listing of your organization's official annual or regional meeting, please send us the following information: sponsor, location, inclusive dates, type and number of continuing education credits (if available), and the name, address, and telephone number of the person or group to contact for more information. All notices and changes must be received no later than 120 days before the first day of the month of desired publication and should be addressed to Calendar,* American Journal of Psychiatry, *1400 K St., N.W., Washington, DC 20005. Because of space limitations, only listings of meetings of the greatest interest to* Journal *readers will be included.*

## OCTOBER

October 1–7, Joint Meeting Between the American Psychiatric Association and the German Society of Psychiatry and Nervous Diseases, Mainz, Mannheim, Heidelberg, Munich, and Bad Kissingen. Contact Ellen Mercer, Director, Office of International Affairs, American Psychiatric Association, 1400 K Street, NW, Washington, DC 20005; 202-682-6286.

October 3–6, annual meeting, American Academy for Cerebral Palsy and Developmental Medicine, Orlando, Florida. Contact John A. Hinckley, Executive Director, P.O. Box 11086, Richmond, VA 23230; 804-282-0036.

October 3–7, annual meeting, Southern Psychiatric Association, Washington, DC. Contact Margo S. Adams, Executive Secretary, P.O. Box 10002, Tallahassee, FL 32302; 904-222-8404.

October 4–7, 48th Annual Conference, American Association for Marriage and Family Therapy, Washington, DC. Contact Mark R. Ginsberg, Ph.D., Executive Director, 1717 K Street, NW, Suite 407, Washington, DC 20006; 202-429-1825.

October 5–7, 7th International Conference on Psychonephrology, Psychonephrology 1990, San Francisco. Contact Norman B. Levy, M.D., Department of Psychiatry, New York Medical College, Valhalla, NY 10595; 914-285-8424.

October 6–8, annual meeting, Association of Mental Health Librarians, Denver. Contact Elizabeth P. Emily, President, Highland Hospital Medical Library, P.O. Box 1101, Asheville, NC 28802-1101; 704-254-3201.

October 6–11, annual meeting, American Academy of Pediatrics, Boston. Contact James E. Strain, M.D., Executive Director, P.O. Box 927, Elk Grove Village, IL 60009-0927; 312-288-5005.

October 7–11, Hospital and Community Psychiatry Institute, American Psychiatric Association, Denver. Contact Sandra Hass, H&CP Institute, American Psychiatric Association, 1400 K Street, NW, Washington, DC 20005; 202-682-6092.

October 7–12, annual meeting, American College of Surgeons, San Francisco. Contact Fred C. Spillman, Convention Manager, 55 East Erie Street, Chicago, IL 60610; 312-664-4050.

October 8–11, annual meeting, American Academy of Family Physicians, Dallas. Contact Robert Graham, M.D., Executive Vice-President, 8880 Ward Parkway, Kansas City, MO 64114; 816-333-9700.

October 10–12, International Conference on Current Practices and Future Developments in the Pharmacotherapy of Mental Disorder, Venice, Italy. Contact Centro Congressi Bonsaglio, Via Borromei, 1/a, 20123 Milano, Italy; 2-807766.

October 10–14, annual meeting, American Academy of Clinical Psychiatrists, Boston. Contact Alicia A. Munoz, Executive Secretary, P.O. Box 3212, San Diego, CA 92103; 619-298-4782.

October 11–13, 14th Danube Symposium of Psychiatry, Budapest. Contact MOTESZ Kongressburo, P.O. Box 32, Budapest, H-1361, Hungary.

October 14–17, annual meeting, American Neurological Association, Atlanta. Contact Linda J. Wilkerson, Association Manager, 2221 University Avenue, SE, Suite 350, Minneapolis, MN 55414; 612-378-3290.

October 14–17, The Richmond Fellowship International Meeting on Treatment of the Severely Mentally Ill, Washington, DC. Contact D.A. Sorensen, Ph.D., Executive Director, Richmond Fellowship of America, 322 West 75th Street, New York, NY.

October 14–17, 84th Annual Scientific Assembly of the Southern Medical Association, Nashville, Tennessee. Contact Kathleen McLendon, Southern Medical Association, 35 Lakeshore Drive, Birmingham, AL 35219-0088; 205-945-1840.

October 20–25, annual meeting, Association of American Medical Colleges, San Francisco. Contact Robert G. Petersdorf, M.D., President, One Dupont Circle, NW, Suite 200, Washington, DC 20036; 202-828-0400.

October 21, annual meeting, American Association of Chairmen of Departments of Psychiatry, New York. Contact Jeffrey L. Houpt, M.D., Secretary-Treasurer, Box AF, Emory University School of Medicine, Atlanta, GA 30322; 404-727-5630.

October 24–26, 1st European Congress on the History of Psychiatry and Mental Health Care, 's-Hertogenbosch, The Netherlands. Contact 1st European Congress on the History of Psychiatry and Mental Health Care, c/o Leiden Congress

*(Continued on page A25)*

**PAMELOR®** (nortriptyline HCl)
**BRIEF SUMMARY.**
Please see package insert for full prescribing information.

**Contraindications:** 1) Concurrent use with a monoamine oxidase (MAO) inhibitor, since hyperpyretic crises, severe convulsions, and fatalities have occurred when similar tricyclic antidepressants were used in such combinations; MAO inhibitors should be discontinued for at least two weeks before treatment with Pamelor® (nortriptyline HCl) is started. 2) Hypersensitivity to Pamelor® (nortriptyline HCl), cross-sensitivity with other dibenzazepines is a possibility. 3) The acute recovery period after myocardial infarction.

**Warnings:** Give only under close supervision to patients with cardiovascular disease, because of the tendency of the drug to produce sinus tachycardia and to prolong conduction time; myocardial infarction, arrhythmia, and strokes have occurred. The antihypertensive action of guanethidine and similar agents may be blocked. Because of its anticholinergic activity, nortriptyline should be used with great caution in patients who have glaucoma or a history of urinary retention. Patients with a history of seizures should be followed closely, since nortriptyline is known to lower the convulsive threshold. Great care is required in hyperthyroid patients or those receiving thyroid medication, since cardiac arrhythmias may develop. Nortriptyline may impair the mental and/or physical abilities required for the performance of hazardous tasks, such as operating machinery or driving a car; therefore, the patient should be warned accordingly. Excessive consumption of alcohol may have a potentiating effect, which may lead to the danger of increased suicidal attempts or overdosage, especially in patients with histories of emotional disturbances or suicidal ideation.
The concomitant administration of quinidine and nortriptyline may result in a significantly longer plasma half-life, higher A.U.C. and lower clearance of nortriptyline.
*Use in Pregnancy*—Safe use during pregnancy and lactation has not been established; therefore, in pregnant patients, nursing mothers, or women of childbearing potential, the potential benefits must be weighed against the possible hazards.
*Use in Children*—Not recommended for use in children, since safety and effectiveness in the pediatric age group have not been established.

**Precautions:** Use in schizophrenic patients may result in an exacerbation of the psychosis or may activate latent schizophrenic symptoms; in overactive or agitated patients, increased anxiety and agitation may occur; in manic-depressive patients, symptoms of the manic phase may emerge. Administration of reserpine during therapy with a tricyclic antidepressant has been shown to produce a "stimulating" effect in some depressed patients. Troublesome patient hostility may be aroused. Epileptiform seizures may accompany administration. Close supervision and careful adjustment of dosage are required when used with other anticholinergic drugs and sympathomimetic drugs. Concurrent administration of cimetidine can produce clinically significant increases in the plasma concentrations of the tricyclic antidepressant. Patients should be informed that the response to alcohol may be exaggerated. When essential, may be administered with electroconvulsive therapy, although the hazards may be increased. Discontinue the drug for several days, if possible, prior to elective surgery. The possibility of a suicidal attempt by a depressed patient remains after the initiation of treatment; in this regard, it is important that the least possible quantity of drug be dispensed at any given time. Both elevation and lowering of blood sugar levels have been reported. A case of significant hypoglycemia has been reported in a type II diabetic patient maintained on chlorpropamide (250 mg/day), after the addition of nortriptyline (125 mg/day).

**Adverse Reactions:** *Cardiovascular*—Hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke. *Psychiatric*—Confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia, panic, nightmares; hypomania; exacerbation of psychosis. *Neurologic*—Numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures, alteration in EEG patterns; tinnitus. *Anticholinergic*—Dry mouth and, rarely, associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis; constipation, paralytic ileus; urinary retention, delayed micturition, dilation of the urinary tract. *Allergic*—Skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight); edema (general or of face and tongue), drug fever, cross-sensitivity with other tricyclic drugs. *Hematologic*—Bone marrow depression, including agranulocytosis; eosinophilia; purpura; thrombocytopenia. *Gastrointestinal*—Nausea and vomiting, anorexia, epigastric distress, diarrhea, peculiar taste, stomatitis, abdominal cramps, black-tongue. *Endocrine*—Gynecomastia in the male; breast enlargement and galactorrhea in the female; increased or decreased libido, impotence; testicular swelling; elevation or depression of blood sugar levels; syndrome of inappropriate ADH (antidiuretic hormone) secretion. *Other*—Jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration; flushing; urinary frequency, nocturia; drowsiness, dizziness, weakness, fatigue; headache; parotid swelling; alopecia. *Withdrawal Symptoms*—Though these are not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

**Overdosage:** Toxic overdosage may result in confusion, restlessness, agitation, vomiting, hyperpyrexia, muscle rigidity, hyperactive reflexes, tachycardia, ECG evidence of impaired conduction, shock, congestive heart failure, stupor, coma, and CNS stimulation with convulsions followed by respiratory depression. Deaths have occurred with drugs of this class. No specific antidote is known; general supportive measures are indicated, with gastric lavage. [PAM-Z19—9/1/89]

SANDOZ PHARMACEUTICALS
Corporation, E. Hanover, NJ 07936 (201) 503-7500

# Productive Days... Restful Nights and Pamelor® (nortriptyline HCl)

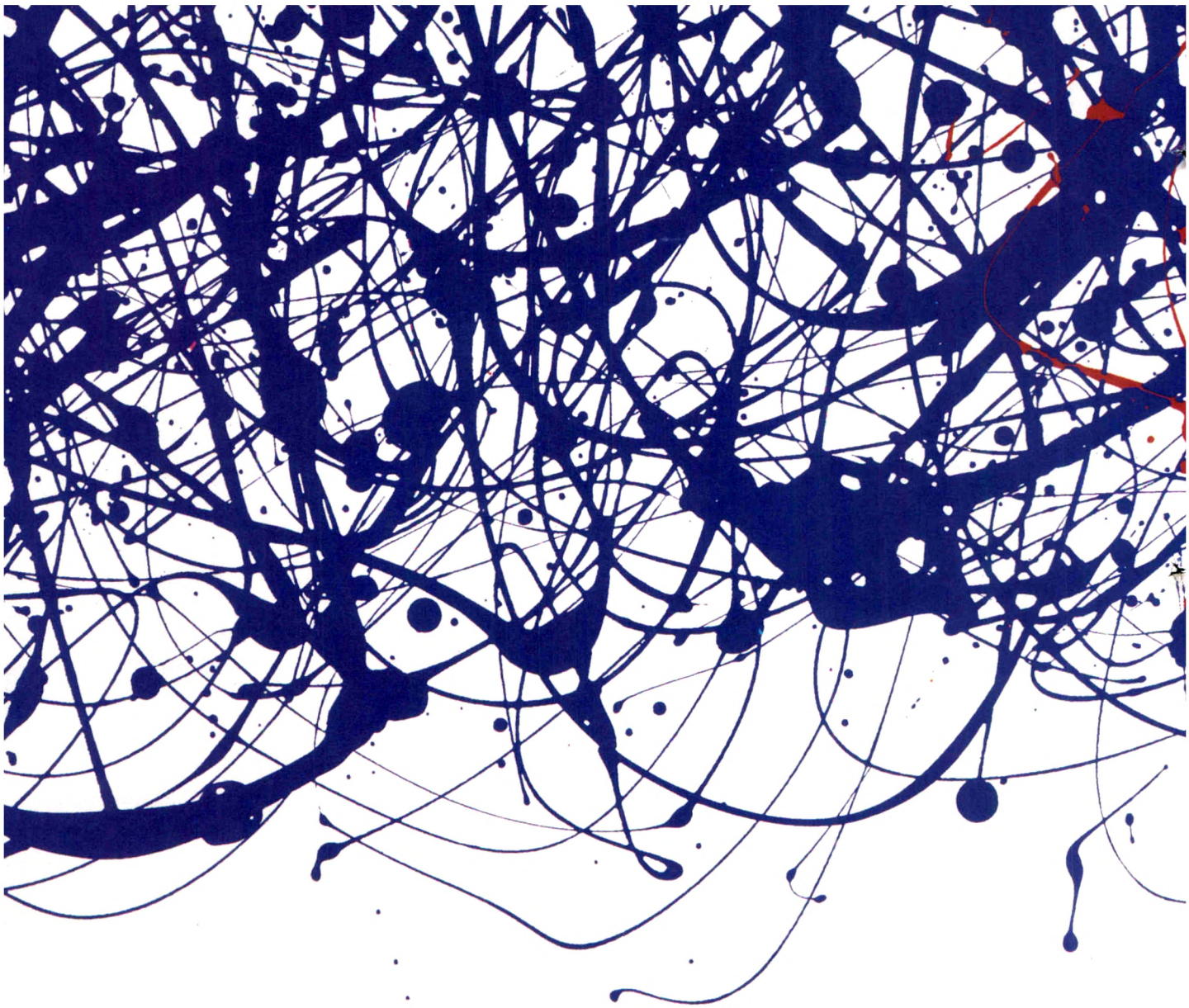
## The Full-Time Antidepressant

### for patients whose symptoms include insomnia and anxiety

# PAMELOR®
## (nortriptyline HCl)

CAPSULES: 10 mg, 25 mg, 50 mg, and 75 mg; SOLUTION: 10 mg/5 mL and alcohol 4%

*The active metabolite of amitriptyline*



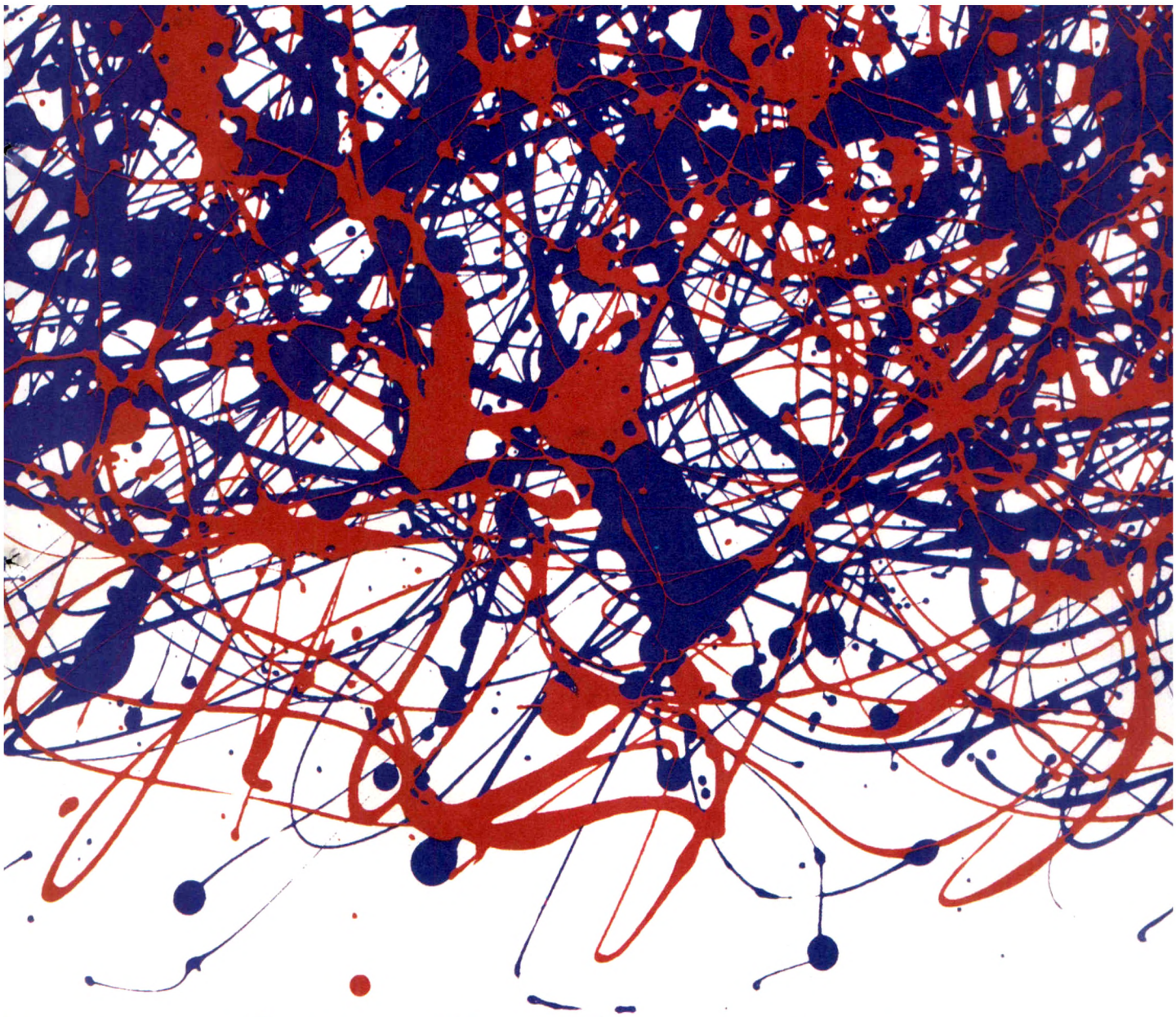
# With depression...

In a clinical trial, XANAX was effective in reducing anxiety symptoms associated with moderate to severe depression.*

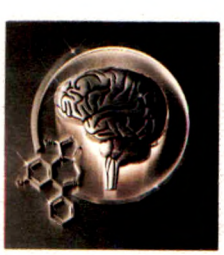
Patients taking XANAX should be alerted to possible additive CNS depressant effects when it is administered with other medications that produce CNS depression.

The usual starting dosage of XANAX is 0.25 to 0.5 mg t.i.d.

*Data on file, The Upjohn Company



# you often find anxiety



TABLETS 0.5 MG

# Xanax®

alprazolam C-IV

## For anxiety associated with depression

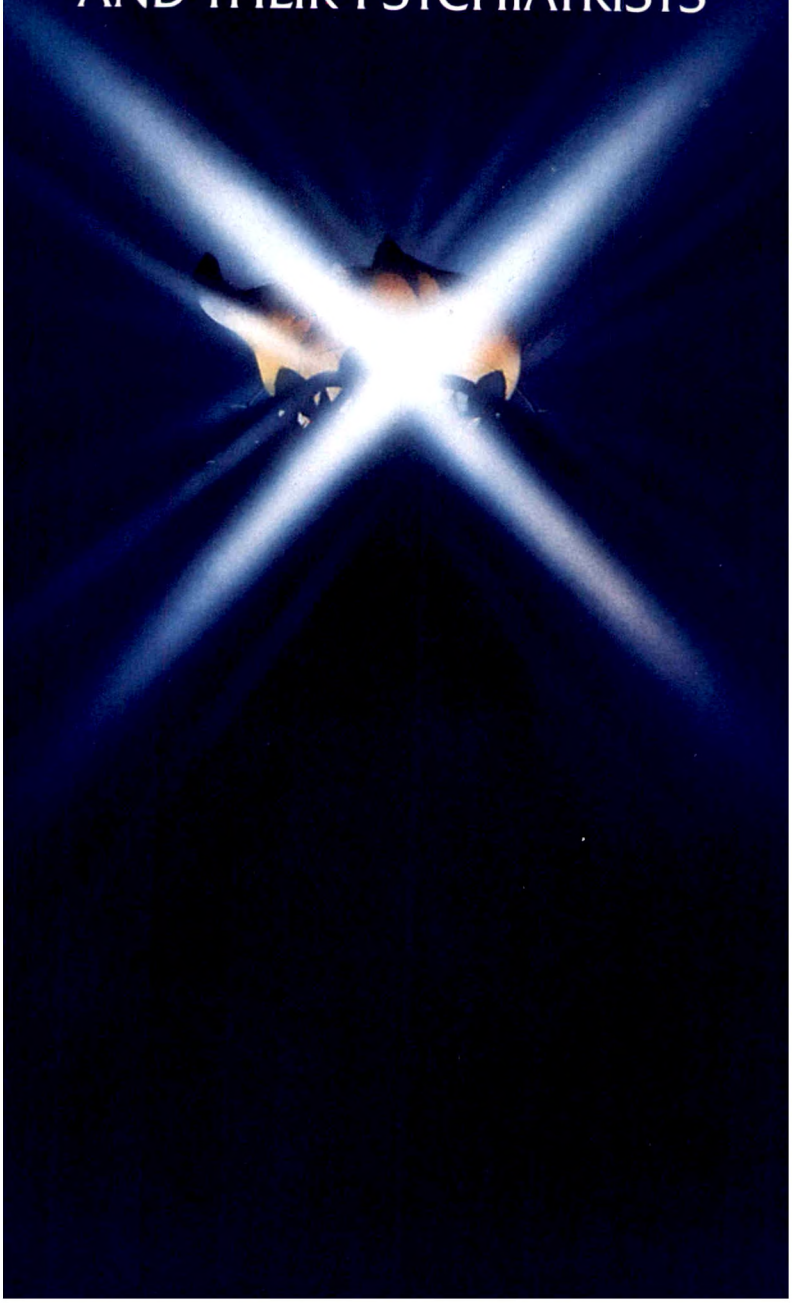
**Upjohn** Please see adjacent page for brief summary of prescribing information.

The Upjohn Company
Kalamazoo, Michigan 49001, USA

INTRODUCING

# A BEACON OF HOPE

FOR THOUSANDS
OF PROBLEM SCHIZOPHRENIC
PATIENTS
AND THEIR PSYCHIATRISTS



# CLOZARIL®
## (clozapine)

SUPERIOR
ANTIPSYCHOTIC
EFFICACY
THAT
GIVES HOPE
FOR
A
NEW
BEGINNING

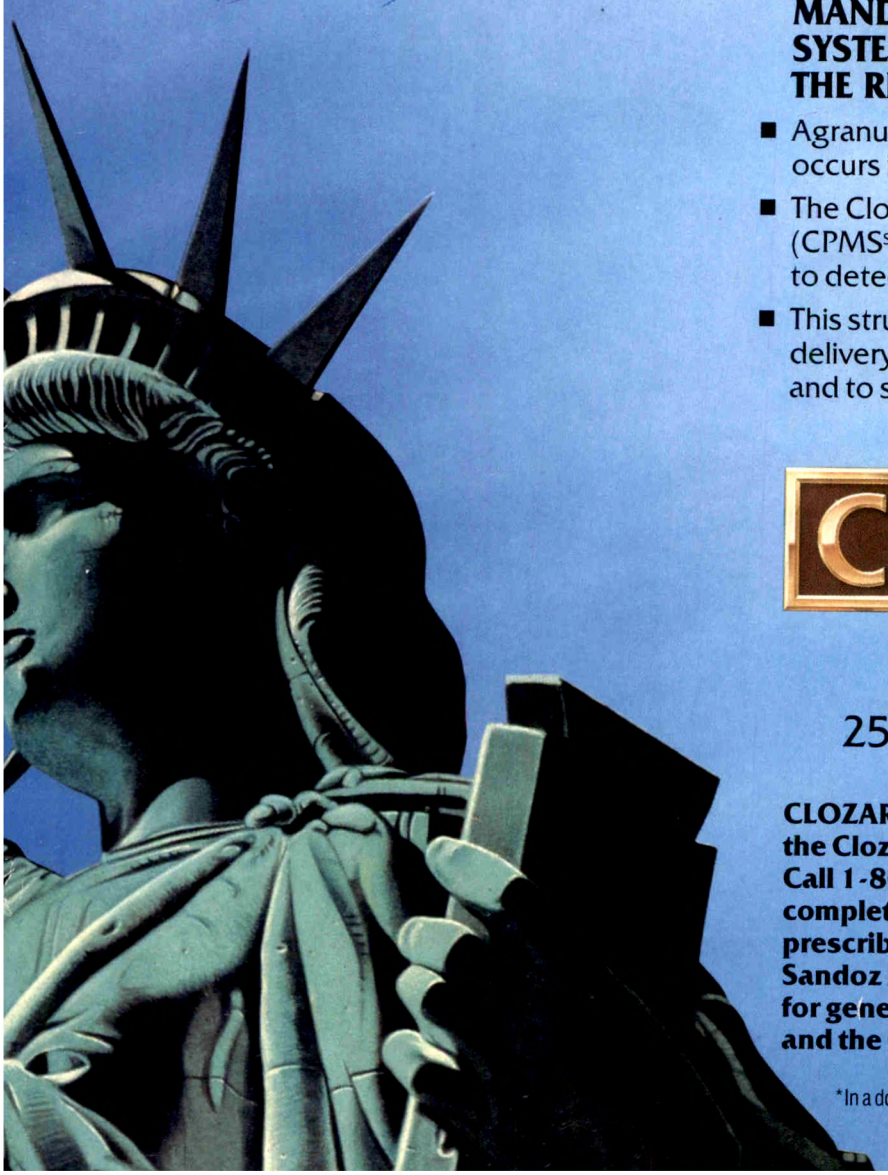
Please see brief summary of prescribing information following this advertisement.

## HOPE BEGINS WITH SUPERIOR SYMPTOMATIC CONTROL*

In a six-week controlled study in severely ill ("problem") schizophrenic patients who failed to respond adequately to treatment with appropriate courses of standard antipsychotic drugs:

- CLOZARIL® (clozapine) succeeded after standard antipsychotics, including haloperidol, failed
- Thirty percent of CLOZARIL patients experienced dramatic global improvement in only six weeks (as determined by the study's rigorous efficacy criteria) vs only 4% of patients receiving chlorpromazine
- Efficacy in both positive and negative symptomatology

P 24, 376



## HOPE CONTINUES WITH A VIRTUAL ABSENCE OF CERTAIN ACUTE EXTRAPYRAMIDAL SYMPTOMS

- CLOZARIL® (clozapine) is indicated for patients intolerant of standard antipsychotics
- No confirmed cases of tardive dyskinesia in over 15 years' worldwide experience
- Side effects that have been reported include: agranulocytosis (1–2%), transient sedation (39%), hypersalivation (31%), tachycardia (25%), constipation (14%), hypotension (9%), hypertension (4%) and weight gain (4%)†
- CLOZARIL use is associated with a substantial risk of seizure, an apparently dose-dependent reaction affecting 1–2% of patients at low doses (below 300 mg/day), 3–4% at moderate doses, and 5% at high doses (600–900 mg/day)‡

## HOPE IS MAINTAINED THROUGH A MANDATORY WBC MONITORING SYSTEM WHICH HELPS MANAGE THE RISK OF AGRANULOCYTOSIS

- Agranulocytosis, a potentially fatal disorder, occurs in 1–2% of patients
- The Clozaril Patient Management System℠ (CPMS℠) was created as an efficient means to detect developing agranulocytosis
- This structured weekly monitoring and drug delivery system helps to protect the patient and to support the physician

CLOZARIL®

(clozapine)

25 mg and 100 mg tablets

**CLOZARIL therapy is available only through the Clozaril Patient Management System. Call 1-800-237-CPMS (2767) or mail in a completed CPMS patient enrollment form to prescribe CLOZARIL (clozapine). Contact your Sandoz Mental Health Sales Representative for general information on CLOZARIL (clozapine) and the Clozaril Patient Management System.**

*In a double-blind study of CLOZARIL (clozapine) versus chlorpromazine encompassing 268 patients, all of whom had first failed on at least three standard antipsychotics over a five-year period and then

INTRODUCING

# CLOZARIL®

## (clozapine)

## A BEACON OF HOPE FOR PROBLEM SCHIZOPHRENIC PATIENTS

**To prescribe CLOZARIL (clozapine) call 1-800-237-CPMS (2767) or mail in a completed CPMS patient enrollment form.**

†Tachycardia, hypotension and hypertension are the principal cardiovascular effects associated with CLOZARIL (clozapine).

‡Because of the substantial risk of seizure associated with CLOZARIL use, a dosage ceiling of 600 mg/day is recommended, although some patients may require up to 900 mg/day for a therapeutic effect.

## HOPE FOR A NEW BEGINNING

**CLOZARIL®**

(clozapine)

25 mg and 100 mg tablets

**SANDOZ PHARMACEUTICALS**
Corporation, E. Hanover, NJ 07936 (201) 503-7500

Please see brief summary of prescribing information following this advertisement. Printed in U.S.A. 3/90 CLO-0390-02

# CLOZARIL®
(clozapine)
TABLETS

**CAUTION: Federal law prohibits dispensing without a prescription.**

## CONTRAINDICATIONS

CLOZARIL is contraindicated in patients with myeloproliferative disorders, or a history of CLOZARIL-induced agranulocytosis or severe granulocytopenia. CLOZARIL should not be used simultaneously with other agents having a well-known potential to suppress bone marrow function. As with more typical antipsychotic drugs, CLOZARIL is contraindicated in severe central nervous system depression or comatose states from any cause.

## WARNINGS

### General

**BECAUSE OF THE SIGNIFICANT RISK OF AGRANULOCYTOSIS, A POTENTIALLY LIFE-THREATENING ADVERSE EVENT (SEE BELOW), CLOZARIL SHOULD BE RESERVED FOR USE IN THE TREATMENT OF SEVERELY ILL SCHIZOPHRENIC PATIENTS WHO FAIL TO SHOW AN ACCEPTABLE RESPONSE TO ADEQUATE COURSES OF STANDARD ANTIPSYCHOTIC DRUG TREATMENT, EITHER BECAUSE OF INSUFFICIENT EFFECTIVENESS OR THE INABILITY TO ACHIEVE AN EFFECTIVE DOSE DUE TO INTOLERABLE ADVERSE EFFECTS FROM THOSE DRUGS. CONSEQUENTLY, BEFORE INITIATING TREATMENT WITH CLOZARIL, IT IS STRONGLY RECOMMENDED THAT A PATIENT BE GIVEN AT LEAST TWO TRIALS, EACH WITH A DIFFERENT STANDARD ANTIPSYCHOTIC DRUG PRODUCT, AT AN ADEQUATE DOSE AND FOR AN ADEQUATE DURATION.**

**PATIENTS WHO ARE BEING TREATED WITH CLOZARIL MUST HAVE A BASELINE WHITE BLOOD CELL (WBC) AND DIFFERENTIAL COUNT BEFORE INITIATION OF TREATMENT, AND A WBC COUNT EVERY WEEK THROUGHOUT TREATMENT, AND FOR FOUR WEEKS AFTER THE DISCONTINUATION OF CLOZARIL.**

**CLOZARIL IS AVAILABLE ONLY THROUGH THE CLOZARIL PATIENT MANAGEMENT SYSTEM℠ (CPMS℠).**

### Agranulocytosis

**Agranulocytosis, defined as a granulocyte count (polys + bands) of less than 500 per mm³, has been estimated to occur in association with CLOZARIL use at a cumulative incidence at one year of approximately 1.3%, based on the occurrence of 15 U.S. cases out of 1743 patients exposed to CLOZARIL during its clinical testing prior to domestic marketing. All of these cases occurred at a time when the need for close monitoring of WBC counts was already recognized. This reaction could prove fatal if not detected early and therapy interrupted. While no fatalities have been associated with the U.S. agranulocytosis cases, and all cases have recovered fully, the U.S. sample is too small to reliably estimate the case fatality rate. Of the 112 cases of agranulocytosis reported worldwide in association with CLOZARIL use as of December 31, 1986, 35% were fatal. However, few of these deaths occurred since 1977, at which time the knowledge of CLOZARIL-induced agranulocytosis became more widespread, and close monitoring of WBC counts more widely practiced. Nevertheless, it is unknown at present what the case fatality rate will be for CLOZARIL-induced agranulocytosis, despite strict adherence to the recommendation for weekly monitoring of WBC counts.**

**Treatment should not be initiated if the WBC count is less than 3500 per mm³, or if the patient has a history of a myeloproliferative disorder, or previous CLOZARIL-induced agranulocytosis or granulocytopenia. Patients should be advised to report immediately the appearance of lethargy, weakness, fever, sore throat or any other signs of infection. If, after the initiation of treatment, the total WBC count has dropped below 3500 per mm³ or it has dropped by a substantial amount from baseline, even if the count is above 3500 per mm³, or if immature forms are present, a repeat WBC count and a differential count should be done. If subsequent WBC counts and the differential count reveal a total WBC count between 3000 and 3500 per mm³ and a granulocyte count above 1500 per mm³, twice weekly WBC counts and differential counts should be performed.**

**If the total WBC count falls below 3000 per mm³ or the granulocyte count below 1500 per mm³, CLOZARIL therapy should be interrupted and patients should be carefully monitored for flu-like symptoms or other symptoms suggestive of infection. CLOZARIL therapy may be resumed if no symptoms of infection develop, and if the total WBC count returns to levels above 3000 per mm³ and the granulocyte count returns to levels above 1500 per mm³. However, in this event, twice-weekly WBC counts and differential counts should continue until total WBC counts return to levels above 3500 per mm³.**

**If the total WBC count falls below 2000 per mm³ or the granulocyte count falls below 1000 per mm³, bone marrow aspiration should be considered to ascertain granulopoietic status. Protective isolation with close observation may be indicated if granulopoiesis is determined to be deficient. Should evidence of infection develop, the patient should have appropriate cultures performed and an appropriate antibiotic regimen instituted.**

**Patients whose total WBC counts fall below 2000 per mm³, or granulocyte counts below 1000 per mm³ during CLOZARIL therapy should *not* be re-challenged with CLOZARIL. Patients discontinued from CLOZARIL therapy due to significant WBC suppression have been found to develop agranulocytosis upon re-challenge, often with a shorter latency on re-exposure. To reduce the chances of re-challenge occurring in patients who have experienced significant bone marrow suppression during CLOZARIL therapy, a single, national master file will be maintained confidentially within the CPMS (Clozaril Patient Management System).**

**Except for evidence of significant bone marrow suppression during initial CLOZARIL therapy, there are no established risk factors, based on worldwide experience, for the development of agranulocytosis in association with CLOZARIL use. However, a disproportionate number of the U.S. cases of agranulocytosis occurred in patients of Jewish background compared to the overall proportion of such patients exposed during the domestic development of CLOZARIL. Most of the U.S. cases occurred within 4-10 weeks of exposure, but neither dose nor duration is a reliable predictor of this problem. No patient characteristics have been clearly linked to the development of agranulocytosis in association with CLOZARIL use, but agranulocytosis associated with other antipsychotic drugs has been reported to occur with a greater frequency in women, the elderly and in patients who are cachectic or have serious underlying medical illness; such patients may also be at particular risk with CLOZARIL.**

**To reduce the risk of agranulocytosis developing undetected, CLOZARIL will be dispensed only within the Clozaril Patient Management System.**

### Seizures

**Seizure has been estimated to occur in association with CLOZARIL use at a cumulative incidence at one year of approximately 5%, based on the occurrence of one or more seizures in 61 of 1743 patients exposed to CLOZARIL during its clinical testing prior to domestic marketing (i.e., a crude rate of 3.5%). Dose appears to be an important predictor of seizure, with a greater likelihood of seizure at the higher CLOZARIL doses used.**

**Caution should be used in administering CLOZARIL to patients having a history of seizures or other predisposing factors. Because of the substantial risk of seizure associated with CLOZARIL use, patients should be advised not to engage in any activity where sudden loss of consciousness could cause serious risk to themselves or others, e.g., the operation of complex machinery, driving an automobile, swimming, climbing, etc.**

### Adverse Cardiovascular Effects

Orthostatic hypotension can occur with CLOZARIL treatment, especially during initial titration in association with rapid dose escalation, and may represent a continuing risk in some patients. Tachycardia, which may be sustained, has also been observed in approximately 25% of patients taking CLOZARIL, with patients having an average increase in pulse rate of 10-15 bpm. The sustained tachycardia is not simply a reflex response to hypotension, and is present in all positions monitored. Either tachycardia or hypotension may pose a serious risk for an individual with compromised cardiovascular function. A minority of CLOZARIL-treated patients experience ECG repolarization changes similar to those seen with other antipsychotic drugs, including S-T segment depression and flattening or inversion of T waves, which all normalize after discontinuation of CLOZARIL. The clinical significance of these changes is unclear. However, in clinical trials with CLOZARIL, several patients experienced significant cardiac events, including ischemic changes, myocardial infarction, nonfatal arrhythmias and sudden unexplained death. Causality assessment was difficult in many of these cases because of serious preexisting cardiac disease and plausible alternative causes. Rare instances of sudden, unexplained death have been reported in psychiatric patients, with or without associated antipsychotic drug treatment, and the relationship of these events to antipsychotic drug use is unknown. CLOZARIL should be used with caution in patients with known cardiovascular disease, and the recommendation for gradual titration of dose should be carefully observed.

### Neuroleptic Malignant Syndrome

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). No cases of NMS have been attributed to CLOZARIL alone. However, there have been several reported cases of NMS in patients treated concomitantly with lithium or other CNS-active agents.

### Tardive Dyskinesia

A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of treatment, which patients are likely to develop the syndrome.

There are several reasons for predicting that CLOZARIL may be different from other antipsychotic drugs in its potential for inducing tardive dyskinesia, including the preclinical finding that it has a relatively weak dopamine blocking effect and the clinical finding of a virtual absence of certain acute extrapyramidal symptoms, e.g., dystonia. In addition, there have been no confirmed cases of tardive dyskinesia developing in association with CLOZARIL use. Nevertheless, it cannot yet be concluded, without more extended experience, that CLOZARIL is incapable of inducing this syndrome.

## PRECAUTIONS

Because of the significant risk of agranulocytosis and seizure, both of which present a continuing risk over time, the extended treatment of patients failing to show an acceptable level of clinical response should ordinarily be avoided. In addition, the need for continuing treatment in patients exhibiting beneficial clinical responses should be periodically re-evaluated. During CLOZARIL therapy, patients may experience transient temperature elevations above 100.4°F (38°C), with the peak incidence within the first three weeks of treatment. While this fever is generally benign and self-limiting, it may necessitate discontinuing patients from treatment. On occasion, there may be an associated increase or decrease in WBC count. Patients with fever should be carefully evaluated to rule out the possibility of an underlying infectious process or the development of agranulocytosis. In the presence of high fever, the possibility of neuroleptic malignant syndrome (NMS) must be considered. CLOZARIL has very potent anticholinergic effects, and great care should be exercised in using this drug in the presence of prostatic enlargement or narrow angle glaucoma. Because of initial sedation, CLOZARIL may impair mental and/or physical abilities, especially during the first few days of therapy. The recommendations for gradual dose escalation should be carefully adhered to, and patients cautioned about activities requiring alertness. Clinical experience with CLOZARIL in patients with concomitant systemic diseases is limited. Nevertheless, caution is advisable in using CLOZARIL in patients with hepatic, renal or cardiac disease.

### Information for Patients

Patients who are to receive CLOZARIL should be warned about the significant risk of developing agranulocytosis. They should be informed that weekly blood tests are required to monitor for the occurrence of agranulocytosis, and that CLOZARIL tablets will be made available only through a special program designed to ensure the required blood monitoring. Patients should be advised to report immediately the appearance of lethargy, weakness, fever, sore throat, malaise, mucous membrane ulceration or other possible signs of infection. Particular attention should be paid to any flu-like complaints or other symptoms that might suggest infection. Patients should be informed of the significant risk of seizure during CLOZARIL treatment, and they should be advised to avoid driving and any other potentially hazardous activity while taking CLOZARIL. Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration. Patients should notify their physician if they are taking, or plan to take, any prescription or over-the-counter drugs or alcohol. Patients should notify their physician if they become pregnant or intend to become pregnant during therapy. Patients should not breast feed an infant if they are taking CLOZARIL.

# Calendar

*(Continued from page A14)*

Bureau, P.O. Box 16065, 2301 GB Leiden, The Netherlands; 31-071-275-299.

October 24–28, 37th Annual Meeting of the American Academy of Child and Adolescent Psychiatry, Chicago. Contact AACAP Annual Meeting, 3615 Wisconsin Avenue, NW, Washington, DC 20016; 202-966-7300.

October 24–28, annual meeting, World Medical Association, Rancho Mirage, California. Contact Angel Orozco, Executive Director, 28, Avenue des Alpes, 01210 Ferney-Voltaire, France; 50-40-75-75.

October 25–28, annual meeting, American Academy of Psychiatry and the Law, San Diego. Contact Jonas R. Rappeport, M.D., Medical Director, 1211 Cathedral Street, Baltimore, MD 21201; 301-539-0379.

October 27–31, 12th World Congress of Social Psychiatry, World Association for Social Psychiatry, Washington, DC. Contact Eliot Sorel, M.D., Congress President, 2020 K Street, NW, Suite 810, Washington, DC 20006; 202-452-9080.

October 28–November 2, annual meeting, Society for Neuroscience, St. Louis. Contact Nancy Beang, Executive Director, 11 Dupont Circle, NW, Suite 500, Washington, DC 20036; 202-462-6688.

## NOVEMBER

November 4–6, 7th Annual Conference, The Chronic Patient: Care and Treatment, "Issues and Challenges in the 90's," Jacksonville. Contact Ed R. Paat, M.S., University Medical Center, Community Mental Health Center, 655 West 8th Street, Jacksonville, FL 32209; 904-350-6806.

November 6–10, annual meeting, World Association for Social Psychiatry, Washington, DC. Contact John L. Carleton, M.D., 696 Ladera Lane, Santa Barbara, CA 93108-1622; 805-969-1376.

November 8–10, annual meeting, Association for Retarded Citizens of the United States, Tampa, Florida. Contact Alan Abeson, Ed.D., Executive Director, 2501 Avenue J, Arlington, TX 76006; 817-640-0204.

November 11–14, 2nd International Congress on Disorders of Personality, Miami. Contact Erik Simonsen, M.D., Nordvang Hospital, DK-2600 Glostrup, Denmark.

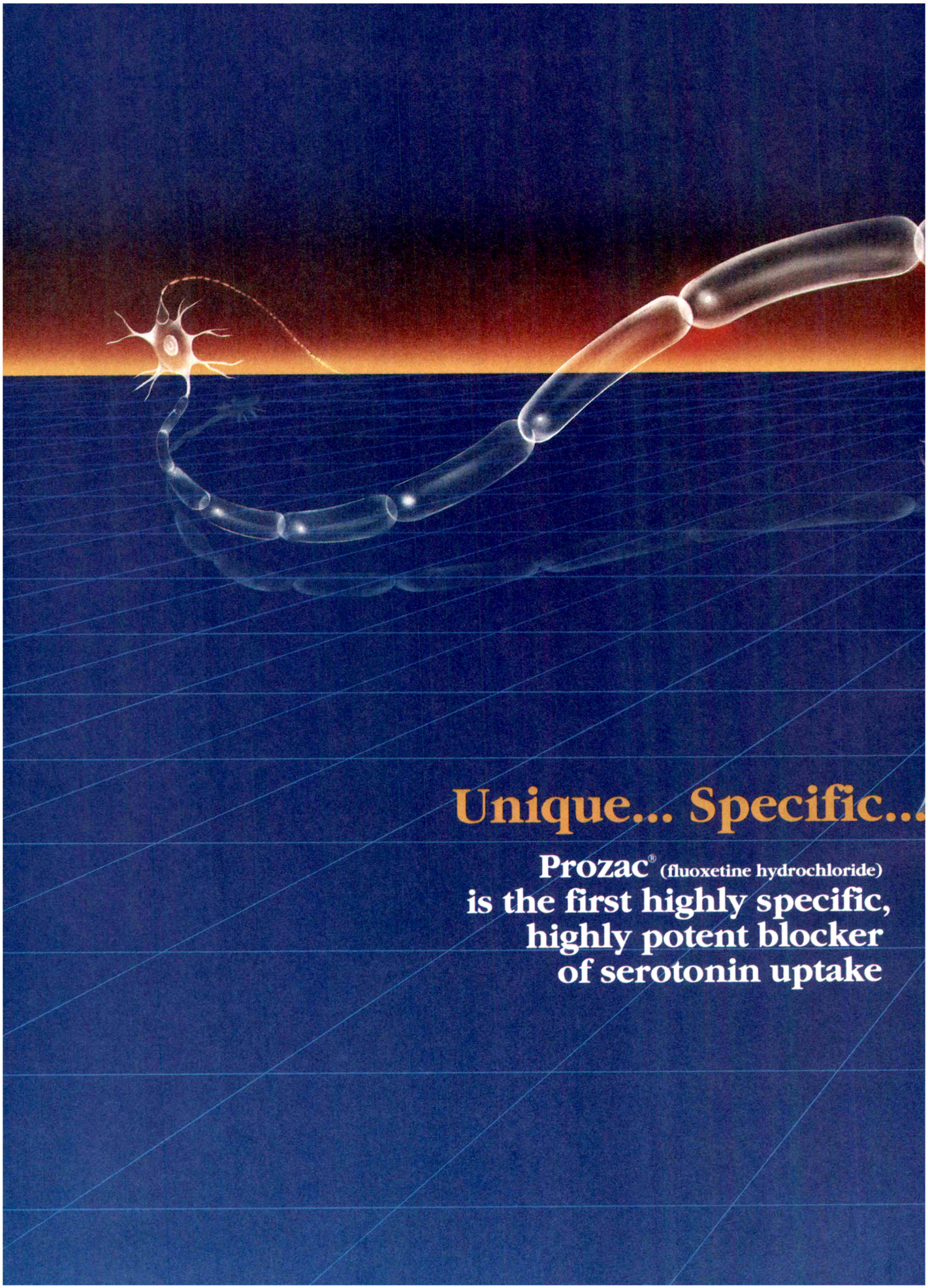
November 13–16, annual conference, Association for Medical Education and Research in Substance Abuse, Rockville, Maryland. Contact Susan Paquin Simpson, AMERSA Conference Coordinator, Brown University Center for Alcohol and Addiction Studies, Box G, Providence, RI 02912; 401-863-3173.

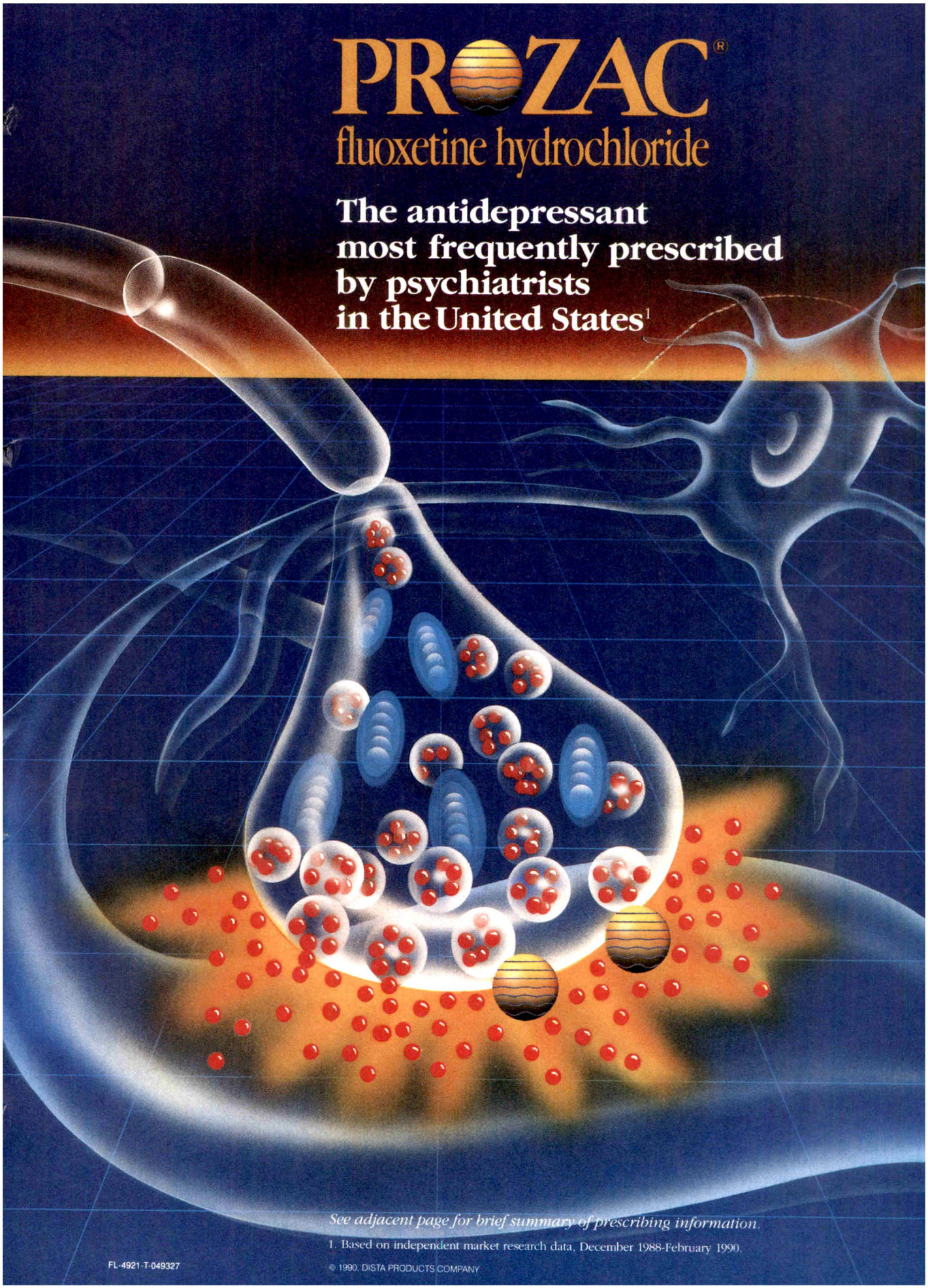
November 13–18, annual meeting, National Mental Health Association, Indianapolis. Contact Preston J. Garrison, Executive Director, 1021 Prince Street, Alexandria, VA 22314; 703-684-7722.

November 15–17, annual meeting, American Academy of Medical Administrators, Nashville, Tennessee. Contact Thomas R. O'Donovan, Ph.D., President, 30555 Southfield Road, Suite 150, Southfield, MI 48076; 313-540-4310.

November 15–18, annual meeting, Academy of Psychosomatic Medicine, Phoenix, Arizona. Contact Evelyne Hallberg, Executive Director, 5824 N. Magnolia, Chicago, IL 60660; 312-784-2025.

November 26–28, International Symposium on Functional Psychiatric Disorders in the Elderly, Melbourne. Contact Associate Professor Edmond Chiu, Department of Psychiatry, St. Vincent's Hospital, Victoria Parade, Fitzroy, Victoria 3065, Australia.


Unique... Specific...
Prozac® (fluoxetine hydrochloride)
is the first highly specific,
highly potent blocker
of serotonin uptake


PROZAC®
fluoxetine hydrochloride
The antidepressant most frequently prescribed by psychiatrists in the United States[1]
See adjacent page for brief summary of prescribing information.
1. Based on independent market research data, December 1988-February 1990.
FL-4921-T-049327
© 1990, DISTA PRODUCTS COMPANY

# Prozac® (fluoxetine hydrochloride)

**Brief Summary.**
**Consult the package insert for complete information.**

**Indications:** For the treatment of depression.

**Contraindication:** Known hypersensitivity to Prozac.

**Warnings:** *Monoamine Oxidase Inhibitors* — The combined use of fluoxetine and MAO inhibitors should be avoided. At least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with fluoxetine.

Because of the long half-lives of fluoxetine and its active metabolite, at least five weeks (approximately five half-lives of norfluoxetine) should elapse between discontinuation of fluoxetine and initiation of an MAOI. Serious events, including death, have been reported to occur following the initiation of an MAOI shortly after discontinuation of fluoxetine.

*Rash and Possibly Allergic Events* — Approximately 4% of 5,600 fluoxetine patients developed a rash and/or urticaria in premarketing testing. Almost a third of these discontinued therapy because of rash and/or associated systemic signs or symptoms. Reported in association with rash were fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved promptly upon discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all were reported to recover completely.

Of two patients who developed a serious cutaneous systemic illness during premarketing clinical trials, one was considered to have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome considered variously to be a vasculitis or erythema multiforme. Other patients have had systemic syndromes suggestive of serum sickness.

Since the introduction of Prozac, systemic events possibly related to vasculitis have developed in patients with rash. Although these events are rare, they may be serious, involving the lung, kidney, or liver. Death has been reported to occur in association with these systemic events.

Anaphylactoid events, including bronchospasm, angioedema, and urticaria alone and in combination, have been reported.

Pulmonary events, including inflammatory processes of varying histopathology and/or fibrosis, have been reported rarely. These events have occurred with dyspnea as the only preceding symptom.

Whether these systemic events and rash have a common underlying cause or represent immunologic responses is not known. Upon the appearance of rash or of other possibly allergic phenomena for which an alternative etiology cannot be identified, Prozac should be discontinued.

**Precautions:** *General* — Anxiety, Nervousness, and Insomnia — Reported by 10% to 15% of patients, 5% of whom discontinued fluoxetine.

Altered Appetite and Weight — Significant weight loss, especially in underweight patients, may be an undesirable result of treatment.

Approximately 9% of fluoxetine patients experienced anorexia in controlled clinical trials, an incidence approximately sixfold that seen with placebo. A weight loss >5% of body weight occurred in 13% of fluoxetine patients compared with 4% in those on placebo and 3% in those on tricyclics. However, only rarely did fluoxetine patients discontinue treatment because of weight loss.

Activation of Mania/Hypomania — Hypomania or mania occurred in approximately 1% of fluoxetine patients in premarketing testing.

Seizures — Twelve of 6,000 patients (0.2%) experienced convulsions (or, possibly, seizures). Prozac should be introduced with care in patients with a history of seizures.

Suicide — Close supervision of high-risk patients should accompany initial therapy. Prescriptions of Prozac should be written for the smallest quantity of capsules consistent with good patient management to reduce the risk of overdose.

The Long Elimination Half-Lives of Fluoxetine and Its Metabolites — Because of the long elimination half-lives of the parent drug (two to three days) and its major active metabolite (seven to nine days), changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment.

Use in Patients with Concomitant Illness — Caution is advisable in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Fluoxetine has **not** been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. ECGs of 312 patients who received Prozac in double-blind trials were retrospectively evaluated; no conduction abnormalities that resulted in heart block were observed. The mean heart rate was reduced by approximately three beats/min.

In subjects with cirrhosis, the clearances of fluoxetine and its active metabolite were decreased. A lower or less frequent dose should be used in patients with cirrhosis.

Fluoxetine should be used with caution in patients with severe renal impairment.In patients with diabetes, Prozac may alter glycemic control. Hypoglycemia has occurred during therapy with Prozac, and hyperglycemia has developed following discontinuation. Insulin and/or oral hypoglycemic dosage may need to be adjusted when fluoxetine therapy is instituted or discontinued.

Interference with Cognitive and Motor Performance — Any psychoactive drug may impair judgment, thinking, or motor skills, and patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug does not affect them adversely.

*Information for Patients* — Physicians should advise their patients to notify them if they:

- are taking or plan to take any prescription or over-the-counter drugs or alcohol
- become pregnant or intend to become pregnant during therapy
- are breast feeding an infant
- develop a rash or hives

*Drug Interactions* — Tryptophan — Five patients receiving tryptophan experienced adverse reactions, including agitation, restlessness, and gastrointestinal distress.

Monoamine Oxidase Inhibitors — See Warnings.

Other Antidepressants — There have been greater than twofold increases of previously stable plasma levels of other antidepressants when Prozac has been administered in combination with these agents.

Lithium — There have been reports of both increased and decreased lithium levels and lithium toxicity. Lithium levels should be monitored.

Diazepam Clearance — The half-life of diazepam may be prolonged in some patients.

Drugs Tightly Bound to Plasma Proteins — Because fluoxetine is tightly bound to plasma protein, the concurrent administration of fluoxetine and another tightly bound drug may cause a shift in plasma concentrations potentially resulting in an adverse effect. Adverse effects may also result from displacement of protein-bound fluoxetine by other tightly bound drugs.

CNS-Active Drugs — Caution is advised if the concomitant administration of Prozac and such drugs is required.

Electroconvulsive Therapy — There have been rare reports of prolonged seizures in patients on fluoxetine receiving ECT treatment.

*Carcinogenesis, Mutagenesis, Impairment of Fertility* — There is no evidence of carcinogenicity, mutagenicity, or impairment of fertility with Prozac.

The dietary administration of fluoxetine to rats and mice for two years at doses approximately 7.5 and 9.0 times the maximum human dose (80 mg) respectively revealed no evidence of carcinogenicity.

Fluoxetine and norfluoxetine have been shown to have no genotoxic effects based on the following assays: bacterial mutation assay, DNA repair assay in cultured rat hepatocytes, mouse lymphoma assay, and in vivo sister chromatid exchange assay in Chinese hamster bone marrow cells.

Two fertility studies in rats at doses approximately five and nine times the maximum human dose (80 mg) respectively revealed no adverse effects on fertility. A slight decrease in neonatal survival was noted, probably associated with depressed maternal food consumption and suppressed weight gain.

*Pregnancy* — Teratogenic Effects — Pregnancy Category B — Reproduction studies in rats and rabbits at doses nine and 11 times the maximum human dose (80 mg) respectively revealed no evidence of harm to the fetus. Although there have been no adequate and well-controlled studies in pregnant women, this drug should be used during pregnancy only if clearly needed.

*Labor and Delivery* — The effect of Prozac on labor and delivery in humans is unknown.

*Nursing Mothers* — Because Prozac is known to be excreted in human milk, caution should be exercised when Prozac is administered to a nursing woman.

*Usage in Children* — Safety and effectiveness in children have not been established.

*Usage in the Elderly* — In clinical studies of several hundred elderly patients, no unusual adverse age-related phenomena were identified. However, these data are insufficient to rule out possible age-related differences during chronic use, particularly in elderly patients with concomitant systemic illnesses or those receiving concomitant drugs.

*Hyponatremia* — Hyponatremia (some cases with serum Na <110 mmol/L) has been reported, which appeared to be reversible on drug discontinuation. Some cases were possibly due to SIADH, and the majority have been in older patients and those taking diuretics or otherwise volume depleted.

*Platelet Function* — There have been rare reports of altered platelet function and/or abnormal results from laboratory studies in patients taking fluoxetine. While there have been reports of abnormal bleeding in several patients taking fluoxetine, it is unclear whether fluoxetine had a causative role.

**Adverse Reactions:** *Commonly Observed* — Nervous system complaints, including anxiety, nervousness, and insomnia; drowsiness and fatigue or asthenia; tremor; sweating; gastrointestinal complaints, including anorexia, nausea, and diarrhea; and dizziness or lightheadedness.

*Associated With Discontinuation of Treatment* — Fifteen percent of 4,000 clinical trial patients discontinued fluoxetine due to an adverse event. The more common events included: psychiatric (5.3%), primarily nervousness, anxiety, and insomnia; digestive (3.0%), primarily nausea; nervous system (1.6%), primarily dizziness; body as a whole (1.5%), primarily asthenia and headache; and skin (1.4%), primarily rash and pruritus.

*Incidence in Controlled Clinical Trials* — The accompanying table enumerates adverse events that occurred at a frequency of ≥ 1% in controlled trials.

TREATMENT-EMERGENT ADVERSE EXPERIENCE INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS

| Body System/ Adverse Event* | Percentage of Patients Reporting Event Prozac (N = 1,730) | Placebo (N = 799) | Body System/ Adverse Event* | Percentage of Patients Reporting Event Prozac (N=1,730) | Placebo (N=799) |
|---|---|---|---|---|---|
| **Nervous** | | | **Body as a Whole** | | |
| Headache | 20.3 | 15.5 | Asthenia | 4.4 | 1.9 |
| Nervousness | 14.9 | 8.5 | Infection, viral | 3.4 | 3.1 |
| Insomnia | 13.8 | 7.1 | Pain, limb | 1.6 | 1.1 |
| Drowsiness | 11.6 | 6.3 | Fever | 1.4 | — |
| Anxiety | 9.4 | 5.5 | Pain, chest | 1.3 | 1.1 |
| Tremor | 7.9 | 2.4 | Allergy | 1.2 | 1.1 |
| Dizziness | 5.7 | 3.3 | Influenza | 1.2 | 1.5 |
| Fatigue | 4.2 | 1.1 | **Respiratory** | | |
| Sedated | 1.9 | 1.3 | Upper respiratory infection | 7.6 | 6.0 |
| Sensation disturbance | 1.7 | 2.0 | Flu-like syndrome | 2.8 | 1.9 |
| Libido, decreased | 1.6 | — | Pharyngitis | 2.7 | 1.3 |
| Light-headedness | 1.6 | — | Nasal congestion | 2.6 | 2.3 |
| Concentration, decreased | 1.5 | — | Headache, sinus | 2.3 | 1.8 |
| **Digestive** | | | Sinusitis | 2.1 | 2.0 |
| Nausea | 21.1 | 10.1 | Cough | 1.6 | 1.6 |
| Diarrhea | 12.3 | 7.0 | Dyspnea | 1.4 | — |
| Mouth dryness | 9.5 | 6.0 | **Cardiovascular** | | |
| Anorexia | 8.7 | 1.5 | Hot flushes | 1.8 | 1.0 |
| Dyspepsia | 6.4 | 4.3 | Palpitations | 1.3 | 1.4 |
| Constipation | 4.5 | 3.3 | **Musculoskeletal** | | |
| Pain, abdominal | 3.4 | 2.9 | Pain, back | 2.0 | 2.4 |
| Vomiting | 2.4 | 1.3 | Pain, joint | 1.2 | 1.1 |
| Taste change | 1.8 | — | Pain, muscle | 1.2 | 1.0 |
| Flatulence | 1.6 | 1.1 | **Urogenital** | | |
| Gastroenteritis | 1.0 | 1.4 | Menstruation, painful | 1.9 | 1.4 |
| **Skin and Appendages** | | | Sexual dysfunction | 1.9 | — |
| Sweating, excessive | 8.4 | 3.8 | Frequent micturition | 1.6 | — |
| Rash | 2.7 | 1.8 | Urinary tract infection | 1.2 | — |
| Pruritus | 2.4 | 1.4 | **Special Senses** | | |
| | | | Vision disturbance | 2.8 | 1.8 |

*Events reported by ≥1% of fluoxetine patients are included.
— Incidence <1%

*Other Events Observed During Premarketing Evaluation in 5,60 Fluoxetine Patients* — Frequent adverse events are defined as thos occurring on one or more occasions in at least 1/100 patients infrequent adverse events are those occurring in 1/100 to 1/1,00 patients; rare events are those occurring in less than 1/1,000 patients

Body as a Whole — *Frequent:* chills; *Infrequent:* chills and feve cyst, face edema, hangover effect, jaw pain, malaise, neck pain, nec rigidity, and pelvic pain; *Rare:* abdomen enlarged, cellulitis hydrocephalus, hypothermia, LE syndrome, moniliasis, and serun sickness.

Cardiovascular System — *Infrequent:* angina pectoris, arrhythmia hemorrhage, hypertension, hypotension, migraine, postura hypotension, syncope, and tachycardia; *Rare:* AV block first-degree bradycardia, bundle-branch block, cerebral ischemia, myocardia infarct, thrombophlebitis, vascular headache, and ventricula arrhythmia.

Digestive System — *Frequent:* increased appetite; *Infrequent* aphthous stomatitis, dysphagia, eructation, esophagitis, gastritis gingivitis, glossitis, liver function tests abnormal, melena, stomatitis thirst; *Rare:* bloody diarrhea, cholecystitis, cholelithiasis, colitis duodenal ulcer, enteritis, fecal incontinence, hematemesis, hepatitis hepatomegaly, hyperchlorhydria, increased salivation, jaundice, live tenderness, mouth ulceration, salivary gland enlargement, stomac ulcer, tongue discoloration, and tongue edema.

Endocrine System — *Infrequent:* hypothyroidism; *Rare:* goiter an hyperthyroidism.

Hemic and Lymphatic System — *Infrequent:* anemia an lymphadenopathy; *Rare:* bleeding time increased, blood dyscrasia leukopenia, lymphocytosis, petechia, purpura, sedimentation rat increased, and thrombocythemia.

Metabolic and Nutritional — *Frequent:* weight loss; *Infrequen* generalized edema, hypoglycemia, peripheral edema, and weight gai *Rare:* dehydration, gout, hypercholesteremia, hyperglycemia hyperlipemia, hypoglycemic reaction, hypokalemia, hyponatremia and iron deficiency anemia.

Musculoskeletal System — *Infrequent:* arthritis, bone pai bursitis, tenosynovitis, and twitching; *Rare:* bone necrosis chondrodystrophy, muscle hemorrhage, myositis, osteoporosis pathological fracture, and rheumatoid arthritis.

Nervous System — *Frequent:* abnormal dreams and agitatio *Infrequent:* abnormal gait, acute brain syndrome, akathisia, amnesia apathy, ataxia, buccoglossal syndrome, CNS stimulation, convulsio delusions, depersonalization, emotional lability, euphoria hallucinations, hostility, hyperkinesia, hypesthesia, incoordinatio libido increased, manic reaction, neuralgia, neuropathy, paranoi reaction, psychosis, and vertigo; *Rare:* abnormal electro encephalogram, antisocial reaction, chronic brain syndrome circumoral paresthesia, CNS depression, coma, dysarthria, dystonia extrapyramidal syndrome, hypertonia, hysteria, myoclonus nystagmus, paralysis, reflexes decreased, stupor, and torticollis.

Respiratory System — *Frequent:* bronchitis, rhinitis, and yawn *Infrequent:* asthma, epistaxis, hiccup, hyperventilation, an pneumonia; *Rare:* apnea, hemoptysis, hypoxia, larynx edema, lun edema, lung fibrosis/alveolitis, and pleural effusion.

Skin and Appendages — *Infrequent:* acne, alopecia, contac dermatitis, dry skin, herpes simplex, maculopapular rash, an urticaria; *Rare:* eczema, erythema multiforme, fungal dermatitis herpes zoster, hirsutism, psoriasis, purpuric rash, pustular rash seborrhea, skin discoloration, skin hypertrophy, subcutaneous nodule and vesiculobullous rash.

Special Senses — *Infrequent:* amblyopia, conjunctivitis, ear pai eye pain, mydriasis, photophobia, and tinnitus; *Rare:* blepharitis cataract, corneal lesion, deafness, diplopia, eye hemorrhage glaucoma, iritis, ptosis, strabismus, and taste loss.

Urogenital System — *Infrequent:* abnormal ejaculation amenorrhea, breast pain, cystitis, dysuria, fibrocystic breas impotence, leukorrhea, menopause, menorrhagia, ovarian disorde urinary incontinence, urinary retention, urinary urgency, urinatio impaired, and vaginitis; *Rare:* abortion, albuminuria, breas enlargement, dyspareunia, epididymitis, female lactation, hematuria hypomenorrhea, kidney calculus, metrorrhagia, orchitis, polyuria pyelonephritis, pyuria, salpingitis, urethral pain, urethritis, urinar tract disorder, urolithiasis, uterine hemorrhage, uterine spasm, an vaginal hemorrhage.

*Postintroduction Reports* — Voluntary reports of adverse event temporarily associated with Prozac that have been received sinc market introduction and which may have no causal relationship wit the drug include the following: cerebral vascular accident, confusio dyskinesia, ecchymoses, gastrointestinal hemorrhage, hyperpro lactinemia, pancreatitis, suicidal ideation, thrombocytopenia, throm bocytopenic purpura, vaginal bleeding after drug withdrawal, an violent behaviors.

**Overdosage**: *Human Experience* — As of December 1987, there wer two deaths among approximately 38 reports of acute overdose wit fluoxetine, either alone or in combination with other drugs and/o alcohol. One death involved a combined overdose with approximate 1,800 mg of fluoxetine and an undetermined amount of maprotilin A second death involved fluoxetine, codeine, and temazepam.

One other patient who reportedly took 3,000 mg of fluoxetin experienced two grand mal seizures that remitted spontaneous without specific anticonvulsant treatment. The actual amount of dru absorbed may have been less due to vomiting.

Nausea and vomiting were prominent in overdoses involving highe fluoxetine doses. Other prominent symptoms of overdose include agitation, restlessness, hypomania, and other signs of CNS excitatio Except for the two deaths noted above, all other overdose case recovered without residua.

A single death attributed to overdose of fluoxetine alone has bee reported.

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***The 150-mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.**

*Please see brief summary of SINEQUAN® (doxepin HCl) prescribing information on next page.*

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**References: 1.** Goldberg HL: Sleep disturbance as a manifestation of depression, in *Somatic Depression: Insights for Primary Care Physicians*. Proceedings of a symposium held in Miami, Dec 4, 1978. New York, Postgraduate Medicine Communications, pp 13-18. **2.** Karacan I, Blackburn AB, Thornby JI, et al: The effect of doxepin HCl (Sinequan) on sleep patterns and clinical symptomatology of neurotic depressed patients with sleep disturbance, in *Sinequan® (doxepin HCl): A Monograph of Recent Clinical Studies*. Princeton, NJ, Excerpta Medica, 1977, pp 4-22. **3.** Goldberg HL, Finnerty RJ: The use of doxepin in the treatment of symptoms of anxiety neurosis and accompanying depression: A collaborative controlled study. *Am J Psychiatry* 1972;129(July):74-77.

# SINEQUAN® (doxepin HCl)

**BRIEF SUMMARY**
**SINEQUAN® (doxepin HCl) Capsules/Oral Concentrate**

**Contraindications.** SINEQUAN is contraindicated in individuals who have shown hypersensitivity to the drug. Possibility of cross sensitivity with other dibenzoxepines should be kept in mind.

SINEQUAN is contraindicated in patients with glaucoma or a tendency to urinary retention. These disorders should be ruled out, particularly in older patients.

**Warnings.** The once-a-day dosage regimen of SINEQUAN in patients with intercurrent illness or patients taking other medications should be carefully adjusted. This is especially important in patients receiving other medications with anticholinergic effects.

***Usage in Geriatrics:*** The use of SINEQUAN on a once-a-day dosage regimen in geriatric patients should be adjusted carefully based on the patient's condition.

***Usage in Pregnancy:*** Reproduction studies have been performed in rats, rabbits, monkeys and dogs and there was no evidence of harm to the animal fetus. The relevance to humans is not known. Since there is no experience in pregnant women who have received this drug, safety in pregnancy has not been established. There has been a report of apnea and drowsiness occurring in a nursing infant whose mother was taking SINEQUAN.

***Usage in Children:*** The use of SINEQUAN in children under 12 years of age is not recommended because safe conditions for its use have not been established.

**Drug Interactions.**

***MAO Inhibitors:*** Serious side effects and even death have been reported following the concomitant use of certain drugs with MAO inhibitors. Therefore, MAO inhibitors should be discontinued at least two weeks prior to the cautious initiation of therapy with SINEQUAN. The exact length of time may vary and is dependent upon the particular MAO inhibitor being used, the length of time it has been administered, and the dosage involved.

***Cimetidine:*** Cimetidine has been reported to produce clinically significant fluctuations in steady-state serum concentrations of various tricyclic antidepressants. Serious anticholinergic symptoms (i.e., severe dry mouth, urinary retention and blurred vision) have been associated with elevations in the serum levels of tricyclic antidepressant when cimetidine therapy is initiated. Additionally, higher than expected tricyclic antidepressant levels have been observed when they are begun in patients already taking cimetidine. In patients who have been reported to be well controlled on tricyclic antidepressants receiving concurrent cimetidine therapy, discontinuation of cimetidine has been reported to decrease established steady-state serum tricyclic antidepressant levels and compromise their therapeutic effects.

***Alcohol:*** It should be borne in mind that alcohol ingestion may increase the danger inherent in any intentional or unintentional SINEQUAN overdosage. This is especially important in patients who may use alcohol excessively.

***Tolazamide:*** A case of severe hypoglycemia has been reported in a type II diabetic patient maintained on tolazamide (1 gm/day) 11 days after the addition of doxepin (75 mg/day).

**Precautions.** Since drowsiness may occur with the use of this drug, patients should be warned of the possibility and cautioned against driving a car or operating dangerous machinery while taking the drug. Patients should also be cautioned that their response to alcohol may be potentiated.

Since suicide is an inherent risk in any depressed patient and may remain so until significant improvement has occurred, patients should be closely supervised during the early course of therapy. Prescriptions should be written for the smallest feasible amount.

Should increased symptoms of psychosis or shift to manic symptomatology occur, it may be necessary to reduce dosage or add a major tranquilizer to the dosage regimen.

**Adverse Reactions. NOTE:** Some of the adverse reactions noted below have not been specifically reported with SINEQUAN use. However, due to the close pharmacological similarities among the tricyclics, the reactions should be considered when prescribing SINEQUAN (doxepin HCl).

*Anticholinergic Effects:* Dry mouth, blurred vision, constipation, and urinary retention have been reported. If they do not subside with continued therapy, or become severe, it may be necessary to reduce the dosage.

*Central Nervous System Effects:* Drowsiness is the most commonly noticed side effect. This tends to disappear as therapy is continued. Other infrequently reported CNS side effects are confusion, disorientation, hallucinations, numbness, paresthesias, ataxia, extrapyramidal symptoms, seizures, tardive dyskinesia, and tremor.

*Cardiovascular:* Cardiovascular effects including hypotension, hypertension, and tachycardia have been reported occasionally.

*Allergic:* Skin rash, edema, photosensitization, and pruritus have occasionally occurred.

*Hematologic:* Eosinophilia has been reported in a few patients. There have been occasional reports of bone marrow depression manifesting as agranulocytosis, leukopenia, thrombocytopenia, and purpura.

*Gastrointestinal:* Nausea, vomiting, indigestion, taste disturbances, diarrhea, anorexia, and aphthous stomatitis have been reported. (See anticholinergic effects.)

*Endocrine:* Raised or lowered libido, testicular swelling, gynecomastia in males, enlargement of breasts and galactorrhea in the female, raising or lowering of blood sugar levels, and syndrome of inappropriate antidiuretic hormone secretion have been reported with tricyclic administration.

*Other:* Dizziness, tinnitus, weight gain, sweating, chills, fatigue, weakness, flushing, jaundice, alopecia, headache, exacerbation of asthma, and hyperpyrexia (in association with chlorpromazine) have been occasionally observed as adverse effects.

*Withdrawal Symptoms:* The possibility of development of withdrawal symptoms upon abrupt cessation of treatment after prolonged SINEQUAN administration should be borne in mind. These are not indicative of addiction and gradual withdrawal of medication should not cause these symptoms.

**Dosage and Administration.** For most patients with illness of mild to moderate severity, a starting daily dose of 75 mg is recommended. Dosage may subsequently be increased or decreased at appropriate intervals and according to individual response. The usual optimum dose range is 75 mg/day to 150 mg/day.

In more severely ill patients higher doses may be required with subsequent gradual increase to 300 mg/day if necessary. Additional therapeutic effect is rarely to be obtained by exceeding a dose of 300 mg/day.

In patients with very mild symptomatology or emotional symptoms accompanying organic disease, lower doses may suffice. Some of these patients have been controlled on doses as low as 25-50 mg/day.

The total daily dosage of SINEQUAN may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed the maximum recommended dose is 150 mg/day. This dose may be given at bedtime. **The 150 mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.**

Anti-anxiety effect is apparent before the antidepressant effect. Optimal antidepressant effect may not be evident for two to three weeks.

**Overdosage.**

A. Signs and Symptoms

1. Mild: Drowsiness, stupor, blurred vision, excessive dryness of mouth.
2. Severe: Respiratory depression, hypotension, coma, convulsions, cardiac arrhythmias and tachycardias.

Also: urinary retention (bladder atony), decreased gastrointestinal motility (paralytic ileus), hyperthermia (or hypothermia), hypertension, dilated pupils, hyperactive reflexes.

B. Management and Treatment

1. Mild: Observation and supportive therapy is all that is usually necessary.
2. Severe: Medical management of severe SINEQUAN overdosage consists of aggressive supportive therapy. If the patient is conscious, gastric lavage, with appropriate precautions to prevent pulmonary aspiration, should be performed even though SINEQUAN is rapidly absorbed. The use of activated charcoal has been recommended, as has been continuous gastric lavage with saline for 24 hours or more. An adequate airway should be established in comatose patients and assisted ventilation used if necessary. EKG monitoring may be required for several days, since relapse after apparent recovery has been reported. Arrhythmias should be treated with the appropriate antiarrhythmic agent. It has been reported that many of the cardiovascular and CNS symptoms of tricyclic antidepressant poisoning in adults may be reversed by the slow intravenous administration of 1 mg to 3 mg of physostigmine salicylate. Because physostigmine is rapidly metabolized, the dosage should be repeated as required. Convulsions may respond to standard anticonvulsant therapy, however, barbiturates may potentiate any respiratory depression. Dialysis and forced diuresis generally are not of value in the management of overdosage due to high tissue and protein binding of SINEQUAN.

**More detailed professional information available on request.**

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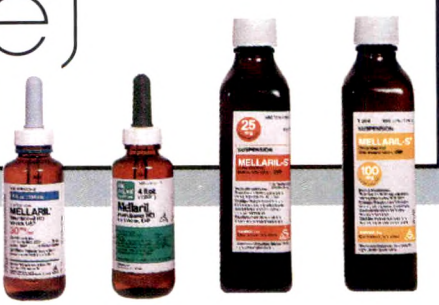


THE AMERICAN JOURNAL OF PSYCHIATRY

*Editorial*

# Utilization Management: Managed or Mangled Psychiatric Care?

Health care today is increasingly managed. Managed care denotes a wide range of organized delivery systems that attempt to balance access, quality, and costs. This balancing act is accomplished by shifting economic risks from the payers to the patients and/or the providers. The balancing of clinical and economic risks between patients and physicians presents a whole set of problems for psychiatric care. This issue is discussed with insight and precision in the article by Gary Tischler elsewhere in this issue of the *Journal.*

Dr. Tischler focuses his comments on utilization management—a specific subset of managed care. Utilization management has been defined by the Institute of Medicine as "a set of techniques used by or on behalf of purchasers of health benefits to manage health care costs by influencing patient care decision-making through case by case assessment of the appropriateness of care prior to its provision" (1, p. 17). This definition emphasizes a case-by-case assessment, distinguishing this approach to health care costs from across-the-board benefit cuts that do not take into account individual patient characteristics. It is also distinguished by the emphasis on prior review, which shifts the focus of utilization review from a retrospective to prospective approach. Utilization management recognizes the physician's central role in prescribing treatment and organizing the production process in medical care. It is the most explicit and direct effort to regulate and control physicians by modifying their decisions. It is therefore a direct intrusion on professional autonomy and judgment. This is the source of most of the resentment of psychiatrists and other physicians toward utilization management approaches.

Dr. Tischler speaks about the limits of utilization management of mental health services. He discusses the role of clinical uncertainty, the limits of substituting outpatient for inpatient services, the shifting of costs from the private to the public sector, and serious confidentiality compromises. He mentions only in passing a specific application of utilization management that may be of great benefit for psychiatric care. A more focused approach called "high-cost case management" concentrates on the relatively few people in any group who generate very large expenditures. The technique of high-cost case management determines whether extra assistance in planning, arranging, or coordinating a specialized treatment plan would permit appropriate, less costly, and high-quality care. If the individual's health insurance plan does not cover these cost-effective options, exceptions can be made to cover these services. These extracontractual benefits can be extremely helpful for the seriously mentally ill individual, who may benefit from additional residential day treatment and outpatient services not ordinarily covered in private health insurance plans.

The vast majority of utilization management, however, has as its objective cost containment pure and simple. The containment of costs benefits the payer and often reflects a decrease in hospital use. The Institute of Medicine, which exhaustively reviewed the research literature and held hearings over a 2-year period, concluded that utilization management has helped reduce inpatient hospital use and limit in-

patient costs. The impact of utilization management on total costs or net costs is much less clear, however. The savings on inpatient care is offset by increased spending for outpatient care and by the administrative costs of utilization management itself. Utilization management has not changed the long-term increase in health care costs. Most important, the Institute of Medicine concluded that systematic evidence about the impact of utilization management on quality is virtually nonexistent. Indeed, it characterized utilization management as a "working hypothesis." It is a working hypothesis that places patients and providers at extraordinary economic and clinical risk. Patients have not given informed consent for this nationwide experiment, which involves millions of people and billions of dollars. Further, the intensity of utilization management is dramatically increasing providers' costs. They are spending more time on managing and copying medical records and on telephone calls with case managers to justify the need for continued care. Often the requests for information come every 3 or 7 days. This has been considered the "cost of doing business," but the profession might need to revise that assumption and begin to bill the fiscal third party for currently nonreimbursable time. This might help prioritize the requests for information and move economic incentives toward the more desirable outcome of providing care rather than providing information.

Utilization management is a fact of life, and as providers, we must cooperate with *reasonable* efforts by payers and purchasers to ensure that payment is for medically appropriate and necessary care. I underscore the word "reasonable" here because I believe we are accountable to our patients in ways that transcend cost considerations and that are the driving force of the utilization management activity. We must challenge and resist unreasonable utilization management procedures and decisions that are aimed solely at cost control and that threaten patient safety, privacy, or the quality of care. We must inform patients about the nature of utilization management and about treatment options in case of adverse utilization management decisions. We may need to use the legal process to sort out the inevitable casualties when conflict results. Above all, as physician psychiatrists we must be advocates for our patients so that they can get needed services, and we must develop and implement cost-effective alternatives in the face of increasingly limited benefits. We must develop standards of practice and participate in research on the efficacy and impact of psychiatric care. Regulation of the utilization management industry is a pressing social policy concern. Standards and criteria used in the utilization management process should be in the public domain, and appeals mechanisms should be clearly described.

As the costs of psychiatric treatment rise, we must carefully assess the damage of cost-containment efforts to quality and access. Our highest ethical obligation is to the patient. How we manage our ethical obligations will determine the level of esteem with which society regards us.

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# Utilization Management of Mental Health Services by Private Third Parties

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*The author describes approaches to utilization management and the growth of this segment of the health care industry. Issues posed for the mental health field by introducing a third party as the arbiter of care include professional uncertainty and the discretionary behavior of practitioners and third parties, the availability of clinically appropriate alternative services, shifting of costs between the public and private sectors, safeguarding privacy, accountability and the integrity of the review process, financial risk versus professional responsibility, and the impact of utilization management on the outcome of care.*

(Am J Psychiatry 1990; 147:967–973)

Health care is a social enterprise that accounts for $11 out of every $100 of goods and services purchased in this nation. Business alone spends over $100 billion yearly on health insurance premiums and payroll tax contributions to the Medicare Hospital Insurance Trust Fund. Confronted by this rapidly expanding segment of the economy, the business community has adopted three major strategies to bring expenditures under control:

1. Shifting economic risk from the payer to the patient and provider through benefit design and pricing strategies.
2. Providing financial incentives to encourage the use of medical care systems that control resource consumption more strictly.
3. Mediating the process of care through utilization management approaches such as preadmission certification, concurrent review, and case management.

Of the three cost-containment strategies, utilization management has the most immediate impact on patient care. A third party is directly interposed between the patient and the provider. Through judgments about the necessity, appropriateness, and adequacy of care, the third party becomes the final arbiter of treatment.

## APPROACHES TO UTILIZATION MANAGEMENT

Utilization management is essentially an adjudicative process. It involves the application of a clinical means test to evaluate the need for treatment and the appropriateness and adequacy of care. The specific approaches used include preadmission certification, concurrent review, and case management.

### *Preadmission Certification*

In confirming the necessity for treatment, preadmission certification takes into account medical/psychiatric, level of functioning, socioenvironmental, and procedural factors. For outpatients, third parties frequently require documentation that a psychiatric condition is associated with a diminished capacity to meet role requirements or carry out activities of daily living. Consideration is given to the potential for exacerbation of an illness that previously resulted in inpatient care or partial hospitalization. The need for physician monitoring of a patient's treatment regimen is also taken into account.

Justification of inpatient care must meet more stringent requirements. The criterion for admission typically is the presence of significant psychiatric symptoms, such as thought disorder, severe depression or anxiety, uncontrolled substance abuse, marked disorganization, or organicity. The extent to which patients

Received Sept. 19, 1989; revision received Dec. 13, 1989; accepted Jan. 11, 1990. From the Department of Psychiatry, Yale University School of Medicine. Address reprint requests to Dr. Tischler, Department of Psychiatry, Yale University School of Medicine, 25 Park St., New Haven, CT 06519.

are dangerous to themselves or others, their ability to care for themselves, and the availability of social supports are weighed. Coexisting medical conditions, impaired impulse control, pathological interactions with the family or social environment, the need for special services or skilled observation, and court mandates are also considered.

Certification for inpatient care usually involves a telephone call to a screening center. Initially most screening was done by people without mental health backgrounds. They used standard questions to solicit information to determine whether preestablished admission criteria were met. With growing emphasis on preadmission certification, private third parties have turned to people with mental health backgrounds to do the screening (e.g., psychiatric nurses, social workers, alcohol abuse counselors). From the perspective of utilization management firms, this facilitates a more pointed inquiry into the circumstances of a proposed admission. It also allows them to adopt a more forceful posture in efforts to induce clinicians to explore alternative treatment arrangements.

*Concurrent Utilization Review and Case Management*

In the mental health field, differences between concurrent utilization review and case management tend to be procedural rather than substantive. Both attempt to answer several interrelated questions regarding inpatient care:

1. Is the treatment plan consistent with the nature and severity of the presenting problem?
2. Given the patient's clinical status, were the diagnostic and therapeutic services consistent with current standards of care and provided in a timely fashion?
3. Have problems occurred that complicated the course of treatment?
4. Is there evidence that the patient is ready to be discharged? If so, are steps being taken to effect discharge?

For outpatient care, the provider submits a treatment plan after an initial consultation or a predetermined number of visits. Additional reports may be required at specified intervals for recertification. Reviewers interact with clinicians, usually by telephone, to clarify treatment issues or query the need for continued care. If questions exist about the adequacy or appropriateness of care, peer reviewers are consulted. They are also used to confirm decisions to terminate payment for treatment.

For inpatients, initial review points are established at the time of admission. It is not uncommon to use regional or hospital-specific norms for this purpose. No consistent method exists for establishing subsequent review intervals. They may be established by the firm as a matter of policy or by reviewers on the basis of their assessment of the patient's clinical status or response to treatment. The assessment of a patient's progress is generally based on information obtained from the treatment plans or telephone contacts with the clinician. Before any action is taken, this information may be evaluated in terms of specific review criteria. As with outpatient review, consultants may be employed to answer questions about the patient's response to treatment. Judgments concerning the care are fed back to the clinician. The feedback may take the form of an action, such as denying coverage for treatment. It may also take the form of a consultation, in which modifications in the treatment plan are proposed.

Although similar to concurrent review, case management is more focused. Case managers often target instances of care characterized by significant treatment complications or little evidence of improvement in clinical status. They are likely to scrutinize cases in which there is evidence of delay in obtaining diagnostic services, desultory implementation of a treatment plan, or the absence of planning for discharge. Where utilization profiles reveal substantial deviations from local or regional norms, case management may focus on specific conditions, settings, or clinicians. For example, in the case of a facility with hospitalization rates and lengths of stay for substance abusers far in excess of regional norms, preadmission certification might be required for all covered individuals seeking admission to that facility for substance abuse. At that time, the reviewer might question whether outpatient care had been considered as an alternative. If not, authorization could be given for outpatient rather than inpatient treatment. Even if inpatient care was authorized, case management might be required. In addition to being more focused, case management is more intrusive than concurrent utilization review. Intervals between contacts are shorter. Case managers may become quite energetic in their quest for "cost-effective" alternatives to a proposed treatment plan. To facilitate discharge planning, they may even assist in arranging for aftercare.

## ISSUES IN UTILIZATION MANAGEMENT

The recent expansion of utilization management activities is as impressive as the level of energy involved in the case management process. Between 1984 and 1987, the proportion of people covered by conventional insurance plans that included preadmission certification increased from under 5% to 44%. If enrollment in conventional plans with preadmission certification and concurrent utilization review is added to enrollment in health maintenance organizations (HMOs) and preferred provider organizations (PPOs), approximately six out of every 10 Americans with group health insurance are in programs with utilization management features. Eleven percent are in PPOs, 16% belong to HMOs, and 32% are in managed fee-for-service plans (1).

The expanded role of utilization management has been accompanied by rapid growth of the segment of

the health care industry providing preadmission certification, concurrent utilization review, and case management services. Only 17 firms listed in a directory published by *Business Insurance* (2) were providing utilization review services in 1978. In 1983 there were 39, over twice as many, and by 1988 there were 93—more than five times as many as in 1978. Thirty-three of the 93 firms furnished information on gross revenues from utilization review activities. The total was approximately $75 million. While incomplete, the figure suggests the potential magnitude of the enterprise. This expanding enterprise poses serious issues for the mental health field.

*Professional Uncertainty and Discretionary Behavior*

The mental health field is characterized by a descriptive nosology and differing models of mental illness. There are many treatment techniques but relatively few rigorous experiments documenting their differential efficacy. These factors make it extremely difficult to achieve consensus among professionals about approaches to treatment. Where expert opinion is significantly divided, values may be construed as evidence. The values may then replace evidence in judgments about the relative merits of specific procedures and practices.

This problem is not unique to psychiatry. The professional uncertainty hypothesis of Wennberg et al. (3) holds that differing beliefs about the value of therapeutic techniques largely explain variations in clinical decision making. Support for the hypothesis comes from the Rand-UCLA Health Services Utilization Study (4). The study demonstrated consistent differences in ratings by surgeons and nonsurgeons of appropriate indications for surgical procedures. Cross-national differences in rating the appropriateness of procedures for diagnosing and treating coronary artery disease have also been documented (5).

Utilization management approaches are vulnerable to professional uncertainty. They rely heavily on normative judgments of what represents appropriate care. When beliefs replace evidence in these judgments, the bias introduced poses an inherent threat to the objectivity and validity of the activity. For example, ratings of a patient's clinical status and the need for psychotherapy have been shown to vary as a function of the clinician's theoretical orientation (6, 7). An example of how such bias affects utilization management is a situation involving long-term inpatient care for a 14-year-old boy with a diagnosis of borderline personality disorder. He had been hospitalized twice previously. The current admission followed a serious suicide attempt. While no longer suicidal, the boy still showed evidence of extreme impulsivity and affective instability. His home situation was erratic, and the possibility of foster care after discharge was being considered. Consequently, the treatment plan included periodic home visits. After review by a case manager, the hospital was informed that the patient met the following criteria for discharge readiness: 24-hour observation and protection not required, reduction in symptoms sufficient to permit continued treatment at another level of care, no unresolved medical/psychiatric complications, and current leaves from the hospital for visits with relatives. Two weeks of extended care were approved to effect discharge. The case had been reviewed by a psychiatric consultant, who concurred with the disposition. However, the consultant was a general psychiatrist whose practice was limited to adults and who had a strong preference for short-term inpatient care when hospitalization was required.

Imprecise communication about the level of professional uncertainty can reinforce the inclination of third parties to exclude care for specific conditions, such as those considered "chronic" or "not amenable to short-term treatment" (8–10). It may also foster attitudes that restrict access to particular services, such as psychiatrically oriented chemical dependency programs (11). The argument that a lack of professional consensus is reasonable given the current level of knowledge is frequently discounted as irrelevant. It has been criticized as nothing more than economically driven obfuscation that is couched in clinical language and intended to forestall implementation of more stringent approaches to utilization management. Apparently, an unspoken function of professional uncertainty is to encourage third parties' discretionary behavior that is aimed at curtailing clinicians' discretionary behavior.

*Securing Appropriate Alternative Services*

A major thrust of utilization management interventions is to reduce lengths of hospital stays by encouraging the use of alternative services. Random assignment studies (12–14) have shown that hospital stays can be shortened when supplemented with aftercare services. They have also demonstrated the effectiveness of substituting community-based programs for inpatient care (15–17). It has been noted (18) that these studies employed sampling strategies which excluded certain groups, such as patients with severe personality disorders, alcohol or drug dependency, or actively homicidal or suicidal behavior. These are the conditions most frequently cited as driving the costs of inpatient mental health care—the adolescent dependent with a profound personality disorder, the patient with both a psychiatric and a substance abuse disorder, and the employee with severe psychosis. If such patients were systematically excluded from studies of alternatives to inpatient care, the ability to generalize from these findings is suspect. This, in turn, raises questions about what represents clinically appropriate substitution.

Substitution is predicated on the availability of alternative services organized to facilitate patient movement and promote continuity of care. Vertical integration and coordinated service delivery, however, are not hallmarks of this enterprise, which has been described as a "de facto system" (19) and a "confederation of services" (20). It also involves enormous geographic

variations in service capacity. While strategies can be developed that encourage substitution, the organizational and resource realities suggest that developing services which ensure clinically appropriate substitution would be costly. Professional disagreement about treatment approaches makes the problem of substitution even thornier. The criteria must be precise in order to provide adequate risk management, e.g., for treating persons judged to be dangerous to themselves or others on an outpatient versus day hospital versus inpatient basis.

The issue of availability is confounded by the lack of mental health coverage for services provided in alternative settings. This may be changing. Expansion of mental health benefits to include services provided by night hospitals, day treatment centers, and halfway houses has been reported (9). Greater flexibility in benefits administration has also been described. This involves waiving benefit restrictions on a case-by-case basis, when a proposed treatment alternative is deemed clinically appropriate (10, 21). Some PPOs have incorporated multilevel residential options as alternatives to inpatient care (22). The usefulness of financing services for high utilizers through capitation is also being explored (23).

*Cost Shifting Between the Public and Private Sectors*

State and local governments bear a far larger share of expenditures for mental health care than for general health care. An estimated 30% of personal mental health expenditures are paid for through state and local government funds, in contrast to 9% of personal medical expenditures (24). In 1985, state mental health agencies allocated more than $8 billion to mental health services. Approximately four out of every five of these dollars came from state government funds (25).

Because of their role in providing and financing mental health care, state mental health agencies are vulnerable to cost-containment initiatives by the federal and private sectors. An indication of that vulnerability is the increased number of transfers to state and county mental hospitals after the initiation of prospective payment (26, 27). Given the current fiscal climate, the ability of state governments to respond to increased service demands is problematic.

Mandated coverage is one way for states to resist private sector efforts to shift costs. Since 1971, 28 states have passed statutes that require private health insurers to underwrite specified coverage for mental health services or offer such benefits as an option; 35 states have similar requirements for alcohol and drug abuse services, and 24 require HMOs to provide such services. Studies indicate that mandated benefits are associated with a shift in payment from patient out-of-pocket or state mental health agency funds to private third-party funds (28, 29). The Employment Retirement Income and Security Act of 1974, however, exempts employers who self-insure from state laws mandating benefits for specific providers, services, or diseases. Thus, employers who self-insure can avoid being subject to state mandates. In 1987, approximately 117 million Americans with employer-provided coverage were enrolled in plans with some aspect of self-insurance (1). Obviously, the issue of cost shifting is quite complex. To the extent that utilization management activities can impose an additional burden on the financial resources and service capacity of state and local governments, it requires careful scrutiny.

*Safeguarding Privacy*

Private third parties demand substantial clinical information from providers but rarely specify their privacy safeguards. Information shared by patients with clinicians can have adverse social consequences. For example, in the case of a person who is being treated for drug dependence, if utilization management reports can be obtained by law enforcement agencies or employers, even the requirement to provide a diagnosis can pose problems. If a requested medical record contains information concerning the patient's drug-taking history or prior involvement with the criminal justice system, the situation is even more volatile.

Most practitioners acknowledge a third party's need to verify claims and to determine whether the services provided are necessary and rendered in accordance with accepted standards of practice. They must still deal with the question of how much or what information is necessary to make these determinations. At the heart of the matter is the question of whether information provided to private review organizations is accessible to others. Federal provisions regarding nondisclosure apply only to organizations with contracts to conduct Medicare review. State statutes, which vary considerably in terms of disclosure provisions, govern organizations engaged solely in private review activities. A number of states have adopted the Model State Statute of Insurance Commissioners (30). Originally designed with arson in mind, the statute is now being applied more broadly. It provides that an insurance carrier may disclose information to law enforcement officials without the consent or knowledge of the insured.

Clinicians are known to respond to the absence of privacy safeguards by reporting diagnoses associated with less stigma and censoring information in the medical record or reports to third parties (31). If that is the case, then utilization management decisions may be based on incomplete or skewed information.

*Accountability and the Integrity of the Review Process*

Proponents of utilization management contend that cost-containment efforts result from a reasonable demand for increased accountability. Few providers argue that accountability is unimportant. In the wake of the burgeoning emphasis on external review, however, they do express serious reservations about the quality

of the review process and its vulnerability to undue emphasis on cost containment, at the expense of quality of care.

Clinicians invariably express misgivings about the criteria or standards for judging care and the qualifications of the people who make these judgments. Practitioners who deal with several external review agencies encounter variable definitions of necessary and appropriate care, but the explicit criteria according to which these determinations are made are rarely divulged. While case management is often described as a "collegial" or "consultative" process, information about the reviewers' professional backgrounds, their qualifications for reviewing mental health care, and in-house training and quality control is treated as proprietary.

Reservations about the vulnerability of the process to excessive emphasis on cost containment focus on the activities of private utilization review firms. These firms employ staff for the specific purpose of providing utilization review/case management services and hire individual consultants to perform peer review. Private review programs such as these are seen as agents of the payer. Quality of care or health outcome indexes are not used to measure the performance of these firms. It is gauged in terms of cost savings, as reflected by claims processed, visits per enrollee, lengths of inpatient stays, or mental health expenditures as a proportion of total health care expenditures.

Perhaps the most extreme position in relation to private third-party review was taken by the American Psychological Association. In testimony before Congress, the association argued that there is an inherent conflict of interest in arrangements of this type and expressed the belief that they should be prohibited by federal law or regulation.

Concerns about conflict of interest and quality control are reinforced by the fact that utilization management firms are not accountable to an impartial authority. How best to achieve accountability is another matter. One approach would be through voluntary adherence to guidelines designed and disseminated by parties with sufficient stature to command the attention of utilization management firms. An alternative approach would be regulation. In 1988, for example, the Maryland House of Delegates passed "An Act Concerning Health Care Utilization Review—Private Review Agents" (HB 960). This statute requires a private review agent to have a certificate of registration to conduct utilization review. It also establishes broad guidelines for evaluating the review process, the qualifications of reviewers, the speed of review, privacy safeguards, consumer/provider feedback, and appeal procedures. The question of accountability was also addressed in *Wickline v. California* (32). In this case, a plaintiff sued the Medicaid program in California, Medi-Cal, alleging that she was injured by a decision of a Medi-Cal consultant which led to premature discharge because it denied coverage for necessary postoperative hospital care. A trial jury awarded $500,000 to the plaintiff, but the verdict was later reversed by the California Court of Appeals. Notwithstanding the holding, the Court of Appeals stated,

> The patient who requires treatment and who is harmed when care which should have been provided is not provided should recover for the injuries suffered from all those responsible for the deprivation of such care, including, when appropriate, health care payers. Third party payers of health care services can be held legally accountable when medically inappropriate decisions result from defects in the design or implementation of cost containment mechanisms as, for example, when appeals made on a patient's behalf for medical or hospital care are arbitrarily ignored or unreasonably disregarded or overridden.

If the opinion is upheld by other courts, then an important precedent has been established and could result in third parties' being held legally accountable for the negligent use of cost-containment mechanisms.

*Financial Risk Versus Professional Responsibility*

Third-party decisions concerning payment for services can place both patient and provider at financial risk. The opinion in *Wickline v. California* makes an important point in relation to this matter: "The physician who complies, without protest with the limitations imposed by a third-party payer, when his medical judgment dictates otherwise, cannot avoid his ultimate responsibility for his patient's care. He cannot point to the health care payer as the liability scapegoat when the consequences of his own determinative medical decisions go sour" (32).

The court's decision clearly implies that cost-containment programs cannot be permitted to impair medical judgment. Providers may elect to comply with review decisions that, in their judgment, are not medically correct. If they do and the patient is injured as a result of the decision, then the practitioner may be found liable of withholding necessary services. Even in the face of pressure to comply with actions by external review organizations that may have adverse financial consequences, clinicians remain ultimately responsible for decisions affecting patients.

*Efficacy of Utilization Management*

Anecdotal testimonies to the efficacy of utilization management abound. After the introduction of preadmission certification and concurrent utilization review programs, for example, Peterson (11) reported a decrease in bed-days per 1,000 enrollees from 120 to 45 days in one health plan and from approximately 130 to 60 in a second. A case management project described by Rodriquez and Maher (33) led to a reduction in average length of inpatient stays of 23% in 1 year, from 29.5 to 22.7 days. Kight (34) related an 18% drop in mental health expenditures to a CHAMPUS demonstration project that included utilization management and preferred provider features. Whether the

savings were attributable to discounting or utilization management, however, was not specified.

While there are many other examples of how utilization management modifies service use and decreases costs, systematic research on the topic is almost entirely lacking (35–39). From 1974 to 1979, for example, the Select Committee on Psychiatric Care and Evaluation (SCOPCE I) reviewed some 1,500 cases at a cost of $250,000. An actuarial study indicated savings of over $5 million. An additional $1 million in savings resulted from the curtailment of inappropriate admissions—a savings-cost ratio of 25:1 (40). The figure reported for CHAMPUS beneficiaries, a group with a high rate of utilization, is remarkably similar to the savings-cost ratio of 28.3:1 reported for firms with high utilization rates in a study of the effects of utilization review programs instituted by a large private insurance carrier (41). It was found in that study that utilization review reduced admissions by 12.3%, inpatient days by 8%, hospital expenditures by 11.9%, and total medical expenditures by 8.3%. For groups with high utilization rates before the program was initiated, the reduction in patient days was 34% and the decrease in hospital expenditures was 30%.

These two studies evaluated utilization review programs in terms of their impact on service utilization and expenditures. Health care outcomes were not considered. To my knowledge, no studies have addressed the effect of utilization management activities on the intermediate or long-term outcome of mental health care.

The most rigorous test would be a randomized trial, with utilization management representing the experimental condition. Using a prospective, longitudinal design, the study would measure differences in clinical status, course of disorder, social functioning, role performance, disposition at discharge, subsequent use of medical, mental health, and social services, and patient satisfaction with the care provided. A less ambitious approach might involve a naturalistic study conducted at several inpatient sites. The sample could be drawn from inpatients with specific conditions of high currency from a utilization management perspective (e.g., schizophrenia, conduct disorder). Rather than attempting to control the intervention, measures could be developed to capture all aspects of the process. These would include quantitative features of the intervention, such as hospital days before first contact or frequency of contacts. Qualitative features, such as whether contacts were on-site or by telephone and whether they were informational or consultative, should also be catalogued. As the intervention proceeds, the responses of the clinician and the patient and family should be rated and the treatment process should be carefully documented. In the evaluation of the association between the activity and treatment outcome, these measures could be aggregated into a categorical typology of utilization management or treated separately as intervening variables.

Research strategies of this type facilitate an assessment of utilization management from a quality-of-care perspective that speaks to aspects of treatment other than its efficiency. By enabling us to link technical aspects of the intervention to their negative and positive consequences, they can also provide guidance for modifying the approach.

## CONCLUSIONS

As health care becomes more specialized, impersonal, and costly, the charismatic image of the physician as artisan/scientist has given way to the more mundane view of the physician as technocrat/philistine. The fabric of Aesculapian authority, which grants the healer the right to probe human minds and bodies in ways permitted to no one else, has become strained. Today, both consumers and purchasers are more knowledgeable about health care, more inclined to question the care provided, and more insistent that the product live up to its claims. The physician is no longer regarded as the sole arbiter of the need for care. Changing economic circumstances and shifting public attitudes have created an ambience supportive of initiatives aimed at altering traditional patterns of health care and increasing the cost consciousness of both providers and patients.

Utilization management is but one among many initiatives introduced with these aims in mind. Of the approaches to cost containment, however, utilization management is the one that challenges a clinician's professional judgment most directly. Freidson (42) identified a profession as "an occupation which has assumed the dominant position in the division of labor, so that it controls the substance of its own work." Thus, professions view themselves as self-directing. Any encroachment or threatened encroachment on their freedom to define a domain of practice is responded to as an assault on the trustworthiness, ethical behavior, and knowledge base that legitimize a profession's unique occupational status. Perhaps this accounts for the visceral quality of the profession's response to utilization management.

What the preceding review of utilization management makes abundantly clear, however, is the pressing need to replace heat with light. The merits of the activity warrant its consideration in terms of more than just economics or resource consumption. Utilization management is an intervention aimed at affecting clinical decision making, and it can have a positive or a negative impact on health status. If we are to be able to make an informed judgment about its merit, we must move beyond description or anecdotal empiricism and evaluate the health-related consequences of the intervention.

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# The Relation of Ulcerative Colitis to Psychiatric Factors: A Review of Findings and Methods

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*The authors reviewed all known English-language literature on the association between psychiatric factors and ulcerative colitis to ascertain the evidence for such an association and evaluate the methods used in these studies. Most of the 138 studies contained serious flaws in research design, such as lack of control subjects, unspecified manner of data collection, and absence of diagnostic criteria. Analysis revealed that methodological flaws were significantly related to the finding of a positive association between psychiatric factors and ulcerative colitis. Seven studies represented solid systematic investigation, and all seven failed to find such an association.*

(Am J Psychiatry 1990; 147:974–981)

Since Murray first observed an association between emotional factors and ulcerative colitis in 1930, a voluminous literature addressing this topic has accumulated. At one time, the debate was whether ulcerative colitis is a psychosomatic condition. Some considered ulcerative colitis to have clear psychosomatic origins (1), while others held it to be a purely physiologic condition (2, 3). Intermediate between these two opposing viewpoints are those who believe that ulcerative colitis has a multifactorial etiology and that emotional aspects are partly involved (4–7), and yet others have suggested that psychological distress in ulcerative colitis may merely be an expected result of any such severe and chronic illness (8–10).

Part of the reason for this disagreement is the paucity of objective and replicable findings in published reports on the subject. This in turn is related to serious deficiencies in research methods. The early studies lacked systematic data collection and control or comparison groups, elements considered essential and basic to medical research. This work was largely theoretical and consisted of isolated case reports and anecdotal findings, from which it was concluded that ulcerative colitis is a psychosomatic disorder. Later investigators accepted those conclusions without challenge (3), even when improved research methods became available. Subsequent research efforts focused on identifying a causative mechanism. The reader is encouraged to review the earlier literature (11–21) to better understand the evolution of this thinking. With this heritage, ulcerative colitis patients have suffered through the years not only with their disease but also with the stigma of the "psychosomatic" label.

In each published article, stated conclusions regarding associations between psychiatric factors and ulcerative colitis influence practicing clinicians who read it. Thus, each report, whether or not it reflects methodologically sound work, helps to shape the general opinion on the topic. In our review we examined all known English-language literature pertaining to this association to see if the conclusions were influenced by the methods employed and if the presence of an association should be considered proven.

## METHOD

### *Selection of Articles*

A computer search generated references for many of the papers on psychiatric and psychological aspects of ulcerative colitis, and a review of *Index Medicus* listings provided more. Additional references were gained by searching through the bibliographies of all articles so obtained, and this process was continued until no further references were uncovered.

To be included as a research paper for review in this article, a report had to specify that the subjects had ulcerative colitis (as opposed to unspecified inflammatory bowel disease) because Helzer et al. (22, 23) have documented very different findings regarding psychiatric factors in ulcerative colitis and Crohn's disease. The size of the study sample also had to be stated explicitly (as opposed to an unspecified number of patients seen over years of experience). The decision was made to include even small studies because these also had an impact on common medical opinion when they were published. If it became apparent from examination of

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the methods of the studies reviewed that the same patient sample (or a subset) was discussed in two or more articles, then these were considered to represent just one study. In such cases, all information was combined into one entry for this analysis, and the number of patients represented the number of nonduplicated subjects from all articles covering that patient subset.

We included an article only if it had been published in English or contained an abstract that had been translated into English and included enough information to meet the criteria. A published abstract not attached to a complete article was not included in this review. A study using a comparison group composed of only subjects with Crohn's disease was considered uncontrolled for the purposes of this review. A study that compared treated and untreated ulcerative colitis subjects but did not have other control subjects was also considered uncontrolled. We constructed a table that listed all studies and selected findings on the association of ulcerative colitis with life events, personality factors, and types and rates of psychiatric disorders reported in each article. (Space limitations prohibit publication here, but this list is available to interested readers on request.)

All available published reviews of articles on this subject were collected by the same methods as those for locating research studies. To be included as a review article for review here, an article had to reference at least three research articles meeting our criteria for inclusion in this study. An article presenting data as well as containing a review, if it met the criteria for inclusion as a study, was listed only with the studies and not with the reviews. An article about ulcerative colitis that contained information on a topic besides ulcerative colitis was included in the review. We constructed a table of review articles and noted the number of studies included in each review, percentage of controlled studies in each review, and the conclusions drawn by the author in regard to the association of ulcerative colitis with life events, personality factors, and psychiatric disorders. (This table is also available to interested readers on request.)

### *Data Analysis*

All papers were carefully reviewed to determine study methods and selected psychiatric conclusions. Then, for a statistical analysis of study conclusions in relation to methods, simple tabulations were performed to determine the number of studies with a particular finding. Studies were segregated according to presence or absence of control groups and the type of control group used (i.e., healthy or medically ill). The control group is so central to sound methods that its absence from a study may be considered sufficient evidence of serious methodological deviation. Because of this, presence or absence of control subjects was the only methodological variable statistically analyzed in this review. Therefore, this computation is merely an example of how methodological factors could affect conclusions and illustrates one facet of our broader methodological critique.

A traditional meta-analysis of this collection of articles (using all patients reported) was not performed because the methods varied too greatly from study to study, and segregation of studies with similar methods would yield categories too small for effective analysis. Instead, we analyzed the data by giving equal weight to all reports and elected not to delete studies with tiny samples (e.g., five or fewer subjects). Particularly in the earlier years a study involving only a few subjects was considered legitimate research, since at that time case reports were more readily accepted as mainstream medical literature. The resultant impression on the reader may have been as great as that from a study of 100 subjects—perhaps even greater considering the emphasis in the past on in-depth studies of individual patients with psychiatric disorders. Separating articles into pre- and post-1970 publication may help identify this effect.

## RESULTS

We located 172 published research reports in our literature search. Thirty-four of these articles were duplicate investigations of the same patients, leaving a total of 138 actual studies under consideration for this review. One group of seven researchers (24–34) was found to have published 11 articles over 35 years on what appeared to be subsets of the same group of patients, which gradually grew over the years to include 136 subjects.

Of the 138 studies, 117 included only adult subjects, 20 included only children, and one study included both. Twenty-five articles were case reports of single patients. The number of subjects ranged from one to 2,000. Thirty-one of the studies sampled only patients referred for psychiatric evaluation and/or treatment.

Only 34 of the 138 studies were controlled, and 19 of these used comparison groups of subjects with medical illness. The remainder used control subjects with "psychosomatic" illnesses, such as irritable bowel syndrome, and/or healthy control subjects.

### *Methodological Observations*

Following are the methodological deficiencies evident in the published literature on psychiatric factors in ulcerative colitis.

1. Sampling—small number of subjects; gastrointestinal diagnosis not appropriately confirmed; subjects with inflammatory bowel disorders not separated according to specific diagnosis; nonrandom, biased selection.

2. Control groups—none; not appropriate; not matched or compared demographically.

3. Data collection—diagnostic criteria not used or not specified; instruments not standardized or lack reliability/validity; lack of blind assessment/assessor

bias; data not comparable across studies; chart review inadequacies; retrospective.

4. Data analysis—not done; not described.

5. Conclusions—unwarranted on the basis of available data; erroneous assumption of causation from mere association.

The first methodological criticisms relate to deficiencies in sampling. It has previously been recognized (3, 8) that the early reports on psychiatric aspects of ulcerative colitis were particularly prone to involve small samples, the most salient examples being the numerous case reports of one or two individuals in psychotherapy. Such tiny samples defy statistical analysis. Reports on larger samples have been criticized for failing to sufficiently describe (35) or to even include (8) statistical data analysis, instead relying on anecdotal reporting based on claims of experience.

Another serious criticism of sampling methods relates to bias. Elsewhere (3) it has been noted that many study samples were composed entirely of subjects referred for psychiatric treatment. Obviously, to begin by selecting a group of psychiatric patients for a study virtually guarantees the finding of a wealth of psychopathology. To avoid selection bias, a consecutive series of ulcerative colitis patients from a nonpsychiatric source is required. A related problem is the failure to sufficiently describe the method of sample selection or randomization procedure (35, 36).

Many early reports were also flawed by failure to describe how the patients were assessed gastroenterologically to confirm the diagnosis of ulcerative colitis, leaving the possibility of impure samples, which may have included patients with irritable bowel syndrome rather than ulcerative colitis. A likely contributor to the assumption that psychological factors have an etiologic role in ulcerative colitis is the possibility of coexistence or confusion of this disorder with irritable bowel syndrome, a condition that has documented psychiatric associations (37, 38). Other authors have suggested that readers conceptualize irritable bowel syndrome and ulcerative colitis as "two aspects or two stages of the same affection" (39).

Another possible contributor to the presumption of psychosomatic illness is the known association of cramping and diarrhea with stress in normal subjects. This same association occurs in patients with ulcerative colitis. Some authors of early studies drew conclusions about ulcerative colitis from studies of gastrointestinal pathophysiology in normal individuals. While it may be tempting to attribute symptoms of normal stress responses and irritable bowel syndrome to ulcerative colitis, this logical flaw would direct researchers to unwarranted conclusions.

Sampling an active clinic population is another methodological error that is particularly relevant in treatment outcome studies. This problem relates to the tendency for patients to consult physicians when they are ill. The statistical phenomenon of regression to the mean would predict that an individual followed over time from an index point of extreme variation from the norm (i.e., starting at the time that the patient visits the physician's office for treatment of a flare-up of gastrointestinal symptoms) will likely have fewer symptoms in the future. Regression to the mean will be especially relevant in ulcerative colitis because this illness is characterized by a chronic course with intermittent relapses (40, 41). Therefore, studies sampling symptomatic patients who visit physicians' offices would be expected to show a decrease in symptoms over time. This improvement could be mistakenly attributed to the experimental treatment applied (e.g., psychotherapy) unless an effect above and beyond that observed in an experimental control (nontreatment) group can be demonstrated or unless statistical allowance for this factor is achieved during data analysis.

A serious but very common methodological fault in studies of psychiatric aspects of ulcerative colitis has been the failure to use proper control subjects or to adequately describe them (35). It has been observed (5, 8) that the early studies generally lacked comparison subjects altogether, although studies without control subjects continue to appear in print even today (42–45). It has been documented (46) that the lifetime prevalence of psychiatric disorder in the general population is about 33%. Therefore, a methodologically equivalent study of ulcerative colitis patients would be expected to show at least this rate by chance alone. Authors of uncontrolled studies who found a lifetime rate of psychiatric disorder in ulcerative colitis patients of <30% (47, 48) and concluded that an association between the two had been shown failed to interpret the data correctly. To draw such a conclusion, they must demonstrate a higher rate of psychiatric disorder than in a similar comparison group without ulcerative colitis.

Even where control groups have been used, other difficulties are apparent. The type of control group used will have substantial effects on study outcome. Comparison of ulcerative colitis patients with a healthy control sample does not permit discrimination between nonspecific psychological effects of chronic illness and psychiatric factors specifically related to ulcerative colitis. Other researchers (8–10) have pointed out that the direction of any relation between inflammatory bowel disease and psychiatric distress could in fact be the reverse of the widely held view, i.e., the vicissitudes of chronic illness may promote psychiatric symptoms and not vice versa. To sort these issues out, studies of psychiatric factors in ulcerative colitis must include control subjects with other chronic medical conditions. In one study (46), individuals with chronic medical illness had a slightly higher lifetime prevalence of psychiatric illness (42%) than that found in a sample of the general population (33%), although Helzer et al. (22) found a rate of only 30% in a sample of medical clinic patients. In a similar vein, it is a methodological mistake to assume that demonstration of an association between psychiatric factors and ulcerative colitis, even with appropriate control subjects, proves causality. Innumerable studies have fallen here.

Although the use of medical control subjects for comparison is essential, even this is not enough. Blind assessment is also necessary, especially given the lingering view of ulcerative colitis as a psychosomatic condition. This notion may bias psychiatric assessment just as a reverse, antipsychological prejudice has been said to do (9). Unfortunately, physician bias may be contagious to patients, who may in turn associate their symptoms with emotional stress or, alternatively, refuse to consider such a connection, either at the direction of their physicians or, sometimes, as they search for meaning on their own (49). Some patient bias may be unavoidable, but it should present a smaller source of error than assessor bias.

Researchers should also gather demographic information about their subjects and control subjects to ensure that the two groups are demographically equivalent (9). For example, certain psychiatric diagnoses occur more frequently in female patients, and failure to address this issue may result in spurious findings of greater psychopathology in the study group if the study group happens to have a predominance of female subjects.

Others have criticized previous studies for using methods of psychiatric assessment that are of uncertain precision (50) or have unproven reliability and validity (9). Sometimes the criteria for emotional evaluation have been only vaguely described or even completely omitted. Researchers have often used their own, previously untested instruments (51, 52). Others have relied on cursory psychological impressions or on a wide variety of nonstandardized personality measures and other scales that permit little cross-study comparison of data. For example, a direct comparison of "alexithymia" (43) with "morbid grief" (53) or with "goal frustration" (54) would be incorrect, yet these terms might reflect similar psychological abnormalities. In addition, some of the psychometric instruments used were not designed for medically ill populations and have confounding medical symptoms in their inventories.

Assumptions about personality traits and psychological conflicts remain largely theoretical, having little relevance to treatment decisions in the individual clinical setting (50). Helzer (50) has emphasized the need to shift our attention from global measures of emotional or personality factors to specific psychiatric diagnoses in conducting psychiatric research. Focusing on specific psychiatric syndromes will permit use of reliable methods in research investigations. It also allows translation of the findings into practical guidelines for clinical management and aids in determining prognosis.

Liedtke et al. (55) pointed out the inadequacy of investigations based on unstructured interviews; information so obtained cannot be compared or reproduced in subsequent studies. Recent years have seen a vast improvement in the objectivity of psychiatric diagnosis due to refinement of diagnostic criteria and application of structured interviews. With these advances in reliability, diagnostic methods in psychiatry now compare favorably with those in other areas of medicine, such as the ECG and radiologic procedures (22).

**TABLE 1. Relation of Use of Control Groups to Findings of Association Between Psychiatric Factors and Ulcerative Colitis**

| Presence or Absence of Association | Number of Controlled Studies[a] | Number of Uncontrolled Studies[a] | Chi-Square Analysis[b] $\chi^2$ (df=1) | p |
|---|---|---|---|---|
| Life events | | | 20.64 | ≤0.0001 |
| Present | 8 | 78 | | |
| Absent | 7 | 3 | | |
| Personality features | | | 18.93 | ≤0.0001 |
| Present | 9 | 66 | | |
| Absent | 9 | 4 | | |
| Psychiatric disorder | | | 19.97 | ≤0.0001 |
| Present | 14 | 73 | | |
| Absent | 14 | 7 | | |

[a]Total number of subjects varies because not all of the 138 studies examined addressed each of the psychiatric factors in the table.
[b]With Yates' correction.

Standardization of diagnostic criteria in psychiatry occurred only as recently as the early 1970s, first with the Feighner criteria (56) and later with the Research Diagnostic Criteria (57) and the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-III*). Diagnostic reliability was further enhanced in the early 1980s with the advent of a *DSM-III*-based structured research interview, the Diagnostic Interview Schedule (DIS) (58). Thus, until very recently, methodologically sound studies were next to impossible because of the lack of objective means of psychiatric assessment.

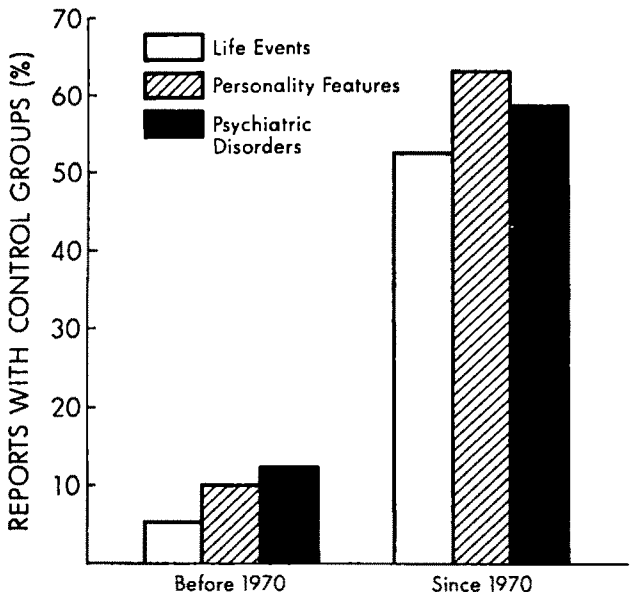
Even when objective diagnostic criteria have been applied to appropriately selected samples with adequate control subjects, comparison of results across studies has not always been possible because some reports have provided information on lifetime prevalences of psychiatric illness, whereas others have reported rates of current psychiatric diagnoses only (59).

Finally, the retrospective nature of almost all the studies on psychiatric aspects of ulcerative colitis has been repeatedly criticized (3, 49, 52). This issue is most crucial in evaluating the relation of life events to the onset of the disease and the timing of subsequent relapses. Retrospective reporting is almost certain to distort recall of events, a notorious problem in all research attempting to determine the relation between life events and medical illness (60, 61). Studies using only medical records as a source of information on patients have been cited for nonuniformity of data and serious omissions (49).

### *Comparative Analysis of Study Conclusions*

In table 1 the data are analyzed according to the presence or absence of control groups. An association

**FIGURE 1. Proportions of Pre- and Post-1970 Reports Indicating Use of Control Groups in Studies of Association Between Psychiatric Factors and Ulcerative Colitis**




between psychiatric variables and ulcerative colitis was found in about half of the controlled studies but in more than 90% of the uncontrolled studies ($p \leq 0.0001$). Comparing the studies that used medically ill control subjects with all the other studies yielded a similar result ($p \leq 0.01$ for all analyses, not shown). Reports of controlled studies were uncommon before 1970 but represent over 50% of the reports published since that time (figure 1).

From our collection of articles, seven reports (22, 59, 62–67) of studies of adult patients with ulcerative colitis were found to contain descriptions of reasonably adequate methods according to the standards discussed earlier in this review. These studies used medically ill control subjects and/or standardized instruments, such as the DIS or the Eysenck Personality Questionnaire (68). The seven studies and their findings are listed in table 2. Although some lacked or had inadequate control groups, their strength lies in the quality of the psychiatric assessments. Four of the studies evaluated personality factors, and a positive association was reported in only one. All seven studies investigated psychiatric diagnoses, and none indicated a positive association. The three studies using specified diagnostic criteria (22, 59, 62, 63) yielded similar rates of psychiatric disorder (25%, 26%, and 34%), all within the range of rates found in populations without ulcerative colitis.

Of the 30 review articles located for this review, the authors of only three (10, 50, 69) failed to conclude that there is an association between ulcerative colitis and life events, personality, or psychiatric disorder. Notably, these three reviews included the two with the highest percentages of controlled studies among the articles reviewed. Helzer's review of five articles (50) covered only studies that were controlled, seven of the 10 articles reviewed by Whitehead and Schuster (10) were controlled, and two of the three studies in Acheson's review (69) were controlled. In no other published review were more than 50% of the studies controlled. Apparently the conclusions in the review articles were also strongly affected by control variables.

## DISCUSSION

When no specific etiology can be found for a condition, as is the case with ulcerative colitis, it is inviting to invoke a psychological explanation. Theoretical models such as the symbolic expression of repressed rage cannot be proved or disproved with standard scientific methods, and hence these ideas stand unchallenged over time. This and other methodological problems can interfere with interpretation of reported findings. For example, statistical errors in 45% to 53% of published medical articles have been described in other reports (35, 36), and in one review (70) it was found that only 28% of a random sample of analytical articles in American medical periodicals had sufficient statistical support for the conclusions drawn.

Thyrotoxicosis and rheumatoid arthritis were formerly included along with ulcerative colitis in the seven classic psychosomatic disorders (11), but with technological advances in medical research we now understand the first two conditions to be physical disorders with no special psychological connections. The terms associated with ulcerative colitis articles have often been vague and cannot be adequately defined or validated by objective measurement, criticisms already raised by others (5, 9). Given such subjective language, it is no surprise that much of the writing on this subject has been speculative and theoretical, based on impressionistic findings, and lacking in systematic data-oriented methods (3, 50, 54).

When this literature review was narrowed to include only controlled studies, the percentage of studies yielding a positive association between psychiatric factors and ulcerative colitis decreased from more than 90% to about 50%, a statistically significant reduction. This analysis showed that imposing the requirement of a control group effectively removed a large portion of the studies reporting a positive association. This maneuver illustrates the importance of applying proper methods when conducting research investigations and the need to scrutinize published studies for adequate methods when examining the literature. Although Helzer (50) did not perform a complete analysis of the type accomplished in this paper, he predicted the findings of this review from his more limited compilation of the relevant literature.

While an association between psychiatric factors and ulcerative colitis was found in about half the controlled studies, many of these studies suffered from other serious methodological deficiencies, e.g., lack of

**TABLE 2. Methodologically Adequate Studies on the Association Between Psychiatric Factors and Ulcerative Colitis**

| Authors and Year | N | Control Groups | Methods of Psychiatric Assessment | Association | |
|---|---|---|---|---|---|
| | | | | Personality Factors | Psychopathology |
| Esler and Goulston, 1973 (64) | 16[a] | Irritable bowel syndrome, medical illness | Institute for Personality and Ability Anxiety Scale Questionnaire, Eysenck Personality Questionnaire | No | No[b] |
| Bellini and Tansella, 1976 (65) | 30[a] | Gastrointestinal illness other than inflammatory bowel disease | Cornell Medical Index, Leyton Obsessional Inventory | No | No |
| Fava and Pavan, 1976–1977 (62, 63) | 20[a] | Gastrointestinal illness other than inflammatory bowel disease | Paykel Life Events Inventory, interview (Feighner criteria) | — | No[b] |
| Helzer et al., 1982 (22) | 50[a] | Medical illness (matched) | Structured interview, Eysenck Personality Questionnaire, Paykel Life Events Inventory (Feighner criteria) | No | No |
| Arapakis et al., 1986 (66) | 37[a] | Irritable bowel syndrome, medical illness | Foulds Personality Deviance Scale, States of Anxiety and Depression Scale | Yes | No |
| Andrews et al., 1987 (59) | 71[a] | None | Spitzer structured interview, Hospital Anxiety and Depression Scale (*DSM-III* criteria) | — | No |
| Tarter et al., 1987 (67) | 27 | Healthy | Diagnostic Interview Schedule (*DSM-III* criteria) | — | No |

[a]Consecutive patients.
[b]Psychopathology evaluation was limited to anxiety and depression.

standardized data collection and absence of diagnostic criteria. Examination of the results of the seven best studies from a methodological standpoint (table 2) revealed that significant psychopathology and prior life events are found in patients with ulcerative colitis no more often than in control subjects.

Investigators who found no association between psychiatric factors and ulcerative colitis have been criticized for spending insufficient interview time or for conducting psychiatric interviews that were too superficial to obtain the necessary information (2, 5) and for failing to search for psychological factors (5, 18). Helzer et al. used structured interviews and found an expected rate of psychopathology in their 50 consecutive ulcerative colitis patients (22) but a 52% lifetime rate of psychiatric diagnoses among Crohn's disease patients, which was significantly higher than the rate for their control subjects (23). This finding argues against the criticism that systematic data collection fails to detect significant psychopathology.

In recent years, the utility of the concept of psychosomatic disease has been seriously questioned (3) to the point that it may have become obsolete (50, 71). Our literature review suggests that formulating the clinical management plan on the basis of a psychosomatic model would be a disservice to ulcerative colitis patients. This is not to suggest that recognizing psychiatric illness is not important. When they occur, psychiatric disorders, such as depression, are frequently overlooked in patients with inflammatory bowel disease (22). Significant morbidity and risk for complications, such as suicide, may be averted by early recognition and appropriate, rigorous treatment of psychiatric disorders in this population, as in any other medical population.

We conclude from this review that methodological errors have biased the published literature on psychiatric factors in ulcerative colitis. Most studies indicating such an association were uncontrolled or otherwise flawed, and the model of ulcerative colitis as a psychosomatic disorder is unsupported by the studies that were methodologically sound. This conclusion can only be reached by understanding the methodological details of the individual reports.

It has been observed that "psychiatric factors, which once dominated reports on ulcerative colitis, rarely are mentioned now" (8). Our comprehensive review, however, has uncovered many of the more recent studies on the etiologic relation of psychiatric factors to ulcerative colitis, and a substantial number of authors continue to subscribe to a psychosomatic model. More controlled studies have appeared in the past two decades, and improved diagnostic techniques for evaluating psychiatric factors have become available and used. These scientific methods are becoming more widely required for determining interactions of psychiatric disorders with medical illness. For now, the reader is urged to forswear unsupported generalizations about the psychiatric aspects of ulcerative colitis and to formulate new ideas based on a critical examination of well-designed studies.

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# Second-Generation Deinstitutionalization, I: The Impact of *Brewster v. Dukakis* on State Hospital Case Mix

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*A 1978 consent decree affecting one region of Massachusetts mandated a drastic reduction of census at its state hospital, where considerable deinstitutionalization had already occurred over the prior two decades. The transfer of patients from hospital to community was to be accomplished through the unprecedented expansion of community resources. This second-generation deinstitutionalization effort achieved substantial census reduction but less than was envisioned. It was most effective in discharging geriatric and mentally retarded patients but far less effective with long-term and new chronic patients, many of whom continue to require repeated hospitalizations despite the availability of a comprehensive array of community-based services.*

(Am J Psychiatry 1990; 147:982–987)

The replacement of state hospital care and treatment with community-based care and treatment has been a fundamental goal of mental health policy for over two decades. The actual implementation of this shift in locus of mental health services has been problematic. Critics have cited numerous difficulties in implementing this policy, including inadequate funding, the failure to develop needed community services, and difficulties in maintaining continuity of care after hospital discharge (1–16). Nonetheless, the doctrine of community-based care persists and has been reinforced through acknowledgment of the rights of the mentally ill to live and receive treatment in the least restrictive setting (17–20).

This sociopolitical movement, referred to as deinstitutionalization (6, 16, 21), forms the background for a legal intervention in Massachusetts in the mid-1970s that would ultimately result in one of the most ambitious efforts ever undertaken to reduce the census of a state hospital by creating community alternatives.

In this paper we review the background of *Brewster v. Dukakis* (22), examine the resulting Northampton Consent Decree (23), and analyze the outcomes. This scrutiny is warranted because the Northampton Consent Decree is a prime example of "second-generation" deinstitutionalization. Unlike the deinstitutionalization efforts of the 1960s and 1970s, the census reduction effort under the Northampton Consent Decree focused on an institution where considerable deinstitutionalization had already occurred. Between 1955 and 1978, the average daily census at Northampton State Hospital declined by roughly 85%, from 2,398 to 368 patients. Those patients who remained in Northampton State Hospital, persons more difficult to sustain in the community, became beneficiaries of this second-generation deinstitutionalization effort. This effort was built upon the allocation of fiscal supports necessary to create the entire range of requisite community services to support a large population of the chronic mentally ill. What are the outcomes of one of the nation's best examples of adequately funded deinstitutionalization?

## BACKGROUND

On Dec. 15, 1976, the plaintiffs in *Brewster v. Dukakis* brought action against the Commonwealth of

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The authors thank the staff of the medical records department of Northampton State Hospital for assistance with data collection and acknowledge the support and assistance provided by Aaron Lazare, M.D.

Massachusetts, "claiming violations of their constitutional and statutory rights to be treated in appropriate, less restrictive alternatives suitable to their needs" (23). This case is a class action suit, David Brewster being the first of nine named plaintiffs representing the class. Members of the class included "all mentally disabled persons who were as of Dec. 15, 1976, are, or may be hospitalized at NSH [Northampton State Hospital]" (23). On Dec. 6, 1978, the parties entered into an agreement in order to establish a comprehensive system of appropriate, less restrictive treatment, training, and support services for each member of this plaintiff class. On Dec. 7, 1978, the agreement became the final Consent Decree upon the approval of the federal district court judge.

The Northampton Consent Decree mandated a reduction in the census at Northampton State Hospital from the 368 patients present on its effective date to 50 by mid-1981; this reduction of 86% was to be accomplished through the creation of 406 new community residential placements (an increase of 263% in capacity) and the provision of appropriate nonresidential services. This mandate assumed a strong relationship between dollars, service systems, and hospital census. Further, it was rooted in the belief that persons with serious mental illness, even those who had been hospitalized for decades, had the ability to adapt to life in a noninstitutional setting. Finally, it was grounded in the principle that

> *a comprehensive community mental health and retardation system* [italics added] consists of three distinct components: (1) residential environments . . . (2) nonresidential treatment, training, and support programs . . . and (3) management services to adequately develop, coordinate, administer, monitor, and evaluate this network of environments and programs. (23, p. 8)

Planning began with detailed assessments of the then current Northampton hospital census as a means of determining the needs of past, present, and future inpatients. These assessments formed the basis for residential program models, some of which were to be more or less permanent placements and some that were to be transitional. Also specified in the Northampton Consent Decree was a range of nonresidential services including case management, crisis intervention, day treatment, vocational rehabilitation, outpatient treatment, and support services.

Compliance with the terms of the Northampton Consent Decree required a massive commitment of resources, the magnitude of which is best assessed by comparing the allocation of resources by the Massachusetts Department of Mental Health to region I (Northampton State Hospital's catchment areas) with allocations to the rest of the state. In fiscal year 1977, region I contained 13.9% of the state's population but received only 9.3% of total mental health resources. However, by fiscal year 1986, region I's share of adult mental health resources had reached 20.3%. Overall, per capita expenditures in fiscal year 1986 for adult, noninpatient services in region I were 138% greater than those for the rest of the state. The major noninpatient expenditures were for residential placements, emergency services, and case management (a major function of which was the development of individual service plans). By design, outpatient treatment received considerably less attention. For example, in each of the five catchment areas in region I, physician input into psychopharmacologic management of all persons who were eligible under the Northampton Consent Decree was to be one three-quarter-time psychiatrist. It was also assumed that only 10% of this population would require any form of psychotherapy. Psychosocial rehabilitation was not strongly emphasized (23).

In fiscal year 1986, at the same time that there was a 138% differential between expenditures for noninpatient services in region I and the rest of the state, the total per capita costs for inpatient services at Northampton State Hospital were only 22% lower than those in the rest of the state inpatient system, despite a much lower average daily census at Northampton State Hospital.

The services actually created in region I under the terms of the Northampton Consent Decree not only met, but in many areas considerably exceeded, the mandates of the decree. The growth in the supply of residential beds is illustrative. Two months before the decree took effect, there were 154 community residential beds in region I. The decree projected a need for a total of 406 new community residential beds. By the end of fiscal year 1986, a total of 664 beds were available in region I—an increase of more than 330% over the number existing just before the decree was signed. The 510 additional beds actually created exceed by 25% the number originally mandated by the decree.

The allocation of these resources and the resulting community service system had profound effects on Northampton State Hospital. The average daily census at the hospital decreased by 49% from the implementation of the decree through 1986 (from 0.45 to 0.24 per 1,000 population). In 1986 the Northampton census (0.24 per 1,000 population) was just over 50% of that in the rest of the inpatient system (0.45) (but it was almost four times greater than the level mandated by the decree for that period [0.06]). The average monthly admission rate at Northampton State Hospital decreased by 40% between 1979 and 1986 and in 1986 was 50% of that in the rest of the Commonwealth. The average monthly first admission rate at Northampton State Hospital decreased by 46% between 1979 and 1986 and in 1986 was 43% of that in the rest of the Commonwealth.

These aggregate data do little to inform us of the nature of the state hospital after the implementation of the decree and the characteristics of the patients who "succeeded" or "failed" in this second-generation deinstitutionalization effort. We address these issues in this paper by comparing Northampton State Hospital with a comparable state hospital that was unaffected by the decree and in part II (24) by examining the

**TABLE 1. Per Capita Resource Allocations by the Massachusetts Department of Mental Health to State Regions for Fiscal Year 1986[a]**

| Type of Mental Health Services | Per Capita Allocation per Region (dollars) | | | Difference From Region I (%) | |
|---|---|---|---|---|---|
| | Region I | Region II | All Regions Except Region I | All Other Regions | Region II Only |
| Total for adults | 48.97 | 34.99 | 30.74 | +59.3 | +39.9 |
| Inpatient | 11.25 | 18.81 | 14.49 | −22.4 | −40.2 |
| Noninpatient | 36.90 | 15.66 | 15.50 | +138.1 | +135.6 |
| Emergency | 4.94 | 2.17 | 1.87 | +164.2 | +127.6 |
| Residential | 15.14 | 4.04 | 3.76 | +302.7 | +274.7 |
| Day treatment | 3.53 | 1.76 | 1.91 | +96.8 | +100.5 |
| Outpatient | 5.52 | 5.58 | 5.28 | +4.5 | −1.0 |
| Vocational | 2.02 | 0.70 | 0.40 | +405.0 | +188.6 |
| Support | 1.98 | 1.32 | 1.42 | +39.4 | +50.0 |
| Case management | 3.76 | 0.08 | 0.85 | +342.4 | +4600.0 |

[a]Figures obtained from the Department of Mental Health Resource Inventory. Sums of individual items may not exactly equal totals because of rounding of per capita estimates.

subsequent psychiatric hospitalization histories of the 368 Northampton patients on the day the decree took effect.

## METHOD

We compared the demographic, diagnostic, and hospital utilization characteristics of the populations at Northampton State Hospital and Worcester State Hospital (which serves region II, an area in many ways similar to region I, but not under the jurisdiction of the Northampton Consent Decree). The comparison of the two hospitals was accomplished in two 1-day point-in-time studies. The first of these assessments was completed 1 year before the decree took effect. The second assessment was completed 7½ years after the decree took effect.

Resource differentials resulting from the Northampton Consent Decree generate a natural experimental design with which to implement the comparisons suggested earlier. Our design employed a pre-post comparison between a treatment group, region I (where the decree was in effect), and a control group, region II (where it was not). The control group was used to account for historical trends not attributable to the decree (25–27).

We chose Worcester State Hospital as our control because region II approximates more closely than any other in Massachusetts the sociodemographic and socioeconomic characteristics of region I. This is illustrated by the close match of the aggregate measures from the federal census of factors widely held to be associated with the need for mental health services (28, 29). (Data are available from the authors.)

Different trends have been observed for acute patients and long-stay patients (27). To account for this, we refined our analysis by comparing the characteristics of the acute (90 days or less) and long-stay (91 days or more) populations at the two hospitals.

## RESULTS

### *Contextual Analysis*

According to 1980 federal census data, region I comprises 13.9% and region II 11.9% of the state's population. In fiscal year 1977 region I received 9.3% and region II 10.6% of the total resources of the department of mental health. When these figures are adjusted for the distribution of the state's population, region II's share of the resources was 33% greater than region I's. By 1986, however, region I received 20.5% of the department's adult resources, while region II received 12.5%. Table 1 shows the fiscal year 1986 allocations for various services in per capita dollars. The per capita spending on noninpatient services in region I was almost 2½ times that in region II. A more detailed look at specific program areas indicates that for many services, differences were even greater, reaching as much as a 4600% differential for case management.

As was the case with the entire state system apart from Northampton State Hospital, the period after the implementation of the Northampton Consent Decree was marked by an increase in the average daily census at Worcester State Hospital. Worcester recorded its lowest postdecree census in 1982, after which time its census began to gradually increase. By the end of fiscal year 1986, the per capita average daily census at Worcester State Hospital was more than double that at Northampton State Hospital (0.59 versus 0.24 per 1,000), and Worcester's per capita admission rate was also nearly twice that at Northampton (0.17 versus 0.10).

### *Total Population*

A comparison of the two point-in-time samples at Worcester and Northampton indicates that the two hospitals were not significantly different with regard to sociodemographic or hospital use patterns in 1977. However, there were significant differences in their diagnostic case mixes. Northampton had a higher per-

centage of patients with schizophrenia than did Worcester (61.7% versus 50.0%), while Worcester had a higher percentage of mentally retarded patients than did Northampton (14.0% versus 7.4%). In 1986, in the postdecree period, Northampton's population had a significantly higher proportion of men than did Worcester's (63.4% versus 54.4%; $\chi^2=4.11$, df=1, p=0.04) and Northampton's patients were significantly younger than Worcester's patients (mean age=40.19 years, range=21–78, versus 48.41, range=19–85; t=−6.10, df=592, p<0.0001, two-tailed test). The diagnostic case mix differences observed in 1977 remained in effect in 1986; Northampton State Hospital's case mix continued to feature fewer patients with organic brain disorders and mental retardation.

Northampton's 1986 hospital utilization rate for persons over age 65 was one-sixth the rate at Worcester State Hospital (0.16 versus 0.92 per 1,000 persons in that age category). The difference in derived utilization rates for younger persons (18 to 64 years old) with primary diagnoses of schizophrenia or affective disorders was considerably less pronounced. The 133 patients at Northampton State Hospital who fell into this category represented a hospital utilization rate of 0.27 per 1,000; this rate was more than half that at Worcester State Hospital, where 201 patients accounted for a derived utilization rate of 0.49 per 1,000.

Additional 1986 between-hospital differences were observed in hospital utilization patterns. The mean number of admissions at Northampton State Hospital was significantly higher than that at Worcester State Hospital (5.84, range=1–16, versus 4.02, range=1–36; t=4.45, df=355, p<0.001, ungrouped two-tailed test). The length-of-stay distribution was significantly skewed toward longer stays in the Worcester sample than in the Northampton sample (D=0.189, p<0.001, Kolmogorov-Smirnov two-tailed test).

### *The Acute Population*

Examination of comparative data on the acute populations of Northampton and Worcester state hospitals in 1977 and 1986 indicates that the main between-period difference between the two hospitals was the change in the proportion of the acute population. In 1977 Northampton's and Worcester's acute patients represented 23% and 18% of the census, respectively, and in 1986, 44% and 36%.

Apart from differences in their relative size, the acute populations of the two hospitals were highly *similar*. No statistically significant differences were observed with regard to the demographic, diagnostic, or hospital utilization characteristics of the two hospitals' acute populations.

### *The Long-Stay Population*

Data comparing the long-stay populations at Northampton and Worcester reveal significant differences in 1986 in age, diagnosis, total prior admissions, and length of stay. Worcester State Hospital's patients were significantly older than Northampton's patients (mean age=52.24 years, range=19–85, versus 40.64, range=21–78; t=6.65, df=363, p<0.0001, two-tailed test), and the percentage of patients over age 65 at Worcester was almost three times that at Northampton (28.6% versus 9.7%).

Schizophrenia was more prevalent at Northampton State Hospital than at Worcester State Hospital (61.0% compared with 53.3%), while organic brain syndrome was more common at Worcester than at Northampton (17.5% versus 7.0%). The overall distribution of cases among the diagnostic categories of schizophrenia, affective disorder, organic brain syndrome, mental retardation, and a residual category consisting of various personality disorders and other diagnoses was significantly different at the two hospitals ($\chi^2=19.01$, df=4, p=0.0008).

The mean number of admissions for Northampton long-stay patients was significantly greater than that for long-stay patients at Worcester (5.81, range=1–23, versus 3.4, range=1–22; t=5.72, df=180, p<0.0001, two-tailed, ungrouped test). In addition, the percentage of Worcester patients who were first admissions was more than twice that for Northampton patients (29.0% versus 13.6%).

Moreover, Worcester's long-stay patients had, on average, been hospitalized longer and included many more patients with extreme lengths of stay. Only two Northampton patients (1.5% of the sample) had been hospitalized continuously for more than 10 years, while 38 of the Worcester long-stay patients (15%) had been hospitalized at least that long. Twelve of these individuals had been continuously hospitalized for over 20 years. In fact, in 1977 the length of stay for Northampton patients was significantly longer than that for Worcester patients; this pattern was dramatically reversed in 1986 (see table 2).

## DISCUSSION

The data presented here show a salient pattern of changes in the case mix of Northampton State Hospital compared to Worcester State Hospital; because of the general comparability of the hospitals and their catchment areas, this change can be directly attributed to the Northampton Consent Decree. These changes have important implications for the allocation of resources to community-based services, as well as for an understanding of the general relationship between community service expansion and the role of the state hospital.

The first set of policy lessons to be drawn from the data derive from differences between the demographic and diagnostic case mix of Northampton State Hospital and Worcester State Hospital. Between 1977 and 1986, Northampton State Hospital virtually eliminated its geriatric population through the placement of patients in nursing homes, the development of special-

**TABLE 2. Lengths of Stay in 1977 and 1986 for Patients Hospitalized for 90 Days or More at Two Massachusetts State Hospitals**

| | 1977[a] | | | | 1986[a] | | | |
|---|---|---|---|---|---|---|---|---|
| | Northampton (N=360) | | Worcester (N=369)[b] | | Northampton (N=125) | | Worcester (N=257) | |
| Length of Stay | N | % | N | % | N | % | N | % |
| 4–11 months | 78 | 21.7 | 75 | 20.3 | 72 | 57.6 | 86 | 33.5 |
| 1–3 years | 92 | 25.6 | 113 | 30.6 | 31 | 24.8 | 84 | 32.7 |
| 4–5 years | 20 | 5.6 | 44 | 11.9 | 14 | 11.2 | 25 | 9.7 |
| 6–10 years | 39 | 10.8 | 51 | 13.8 | 6 | 4.8 | 24 | 9.3 |
| 11–20 years | 46 | 12.8 | 27 | 7.3 | 0 | 0.0 | 26 | 10.1 |
| 21–30 years | 30 | 8.3 | 17 | 4.6 | 1 | 0.8 | 5 | 2.0 |
| 31–40 years | 34 | 9.4 | 22 | 6.0 | 0 | 0.0 | 5 | 2.0 |
| Over 40 years | 21 | 5.8 | 20 | 5.4 | 1 | 0.8 | 2 | 0.8 |

[a]In 1977 the Northampton State Hospital patients had a significantly longer length of stay ($D=0.129$, $p<0.005$, Kolmogorov-Smirnov two-tailed test); in 1986 the Worcester State Hospital patients had a significantly longer length of stay ($D=0.243$, $p<0.001$, Kolmogorov-Smirnov two-tailed test).
[b]Data were missing for six patients.

ized geriatric residential programs, and diversionary efforts that prevented the regrowth of this population. While at Worcester State Hospital the geriatric population in 1986 was somewhat smaller than it had been in 1977, it nevertheless remained a significant presence. A similar pattern was noted for the dual-diagnosed (mentally ill and mentally retarded) population.

A comparable degree of success was not achieved with younger patients. The Northampton population contained fewer young adult chronic patients in 1986 than it had in 1977 or than the Worcester population had at either point. The differences, however, were not remarkable.

Because of finite resources for the creation of community-based residential programs, allocating them to the development of specialized programs for geriatric and dual-diagnosed (mentally ill and mentally retarded) patients who cannot be appropriately placed in nursing homes, hospitals for patients with chronic diseases, or facilities for the developmentally disabled, but who do not need a state hospital, appears warranted. Several benefits accrue. The geriatric and mentally retarded patients themselves are placed in an environment in which they might be less at risk from more assaultive or disruptive psychiatric patients. The removal of geriatric and mentally retarded patients, who often have long, continuous hospitalizations and use a disproportionate number of patient days, can decrease the size of the census and allow more attention to be directed to acute psychiatric treatment. The geriatric and mentally retarded patients who are placed in appropriate community residences, rather than inappropriately remaining on hospital wards, can (theoretically) experience improvements in the quality of their lives. Whether this last point is actually so, or, rather, whether these deinstitutionalized patients are simply residing in pseudo-institutional settings in the community is a crucial, but as yet unanswered, question. The inpatient and residential budget of region I totals $26.39 per capita, greater than region II's ($22.85) or the budget for the state as a whole outside of region I ($18.25). The additional expenditures would be justified if one could demonstrate a related theoretical improvement in quality of life. This is one of the foci of our ongoing research.

A second set of policy lessons concerns expectations regarding the function of the state hospital in a resource-intensive environment. Goldman et al. (30–32) have noted that acute treatment, chronic care, and backing up the entire human services system have been among the state hospital's many functions. These persist nationwide even after two decades of deinstitutionalization (33). The persistence of these functions at Northampton State Hospital indicates that those who propose community service systems like those specified in the Northampton Consent Decree must expect to continue to have available the state hospital or a comparable inpatient facility. The belief expressed in the Northampton Consent Decree that the requirements for newly admitted patients with acute psychopathology and repeat-admission patients with chronic mental illness could be fulfilled by residential environments, nonresidential community services, and general hospitals was simply not borne out.

In addition to the policy implications, it is useful to compare the outcome of the second-generation deinstitutionalization effort in Massachusetts with the outcome of the original (and ongoing) national deinstitutionalization effort. Chief among the many reported outcomes of national deinstitutionalization was a reduction in the size of the state hospital population as less seriously ill patients were discharged to other settings, and many individuals who would have been hospitalized before the deinstitutionalization effort were treated in the community. This left the hospital with a smaller but more seriously disturbed population. As this process continued, the length of hospital stays declined as periods of community living interrupted what in an earlier era would have been the more common long-term hospitalization (34).

The parallels between these outcomes and those of the second generation are striking. Northampton State

Hospital operates no differently than the modal deinstitutionalized state hospital except for its shift in scale. Extensive community resources created a numerical difference, not a functional difference. Northampton State Hospital continues to provide acute treatment but at a lower rate, to render chronic care but at a much lower rate, and to function as a human service system catchall but at a substantially lower rate.

Northampton State Hospital's major exemption from the traditional, global, twentieth-century functions of the state hospital, as indicated by this analysis of state hospital case mix, is the discharge of the geriatric and mentally retarded long-stay patients and their successful maintenance in the community. This exception has powerful implications. It should allow the state hospital to better serve its original function of treating the mentally ill:

> If the insane have done nothing to forfeit the claim which men who suffer have, by the law of nature, upon men who are able to prevent suffering; they should be treated, not with a sole regard to the security of others, but with special reference also to their own misfortune, and in a manner adapted to shorten their duration, or where that is impossible, at least to mitigate their severity. (35)

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# Second-Generation Deinstitutionalization, II: The Impact of *Brewster v. Dukakis* on Correlates of Community and Hospital Utilization

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*On the basis of the principle that patients have the right to be treated in the least restrictive setting appropriate to their needs, all 368 patients at Northampton State Hospital (Massachusetts) were discharged over a 10-year period. Three-quarters were discharged to community settings. Half of the patients were never rehospitalized, but many others continued to display patterns of recidivism. On the assumption that socially dysfunctional behavior would improve after discharge, the funded community system emphasized assessments, residential placements, and crisis intervention and deemphasized treatment. The findings raise many questions about the efficacy and wisdom of attempting to serve an entire state hospital population in the community.*

(Am J Psychiatry 1990; 147:988–993)

The period during which deinstitutionalization has proceeded has been marked by heated debates over the efficacy and appropriateness of community mental health initiatives (1–18). All too often these debates have focused on the global question: deinstitutionalization—yea or nay. The nuances of outcomes and their correlates have been lost amid the rhetoric.

Some cohorts of the chronic mentally ill, such as young adult chronic patients, have seemingly defied many of the efforts to sustain them in the community (19–24). Other subpopulations, less frequently the focus of attention, may have succeeded under available community service modalities. While there are reports on model programs (25–29), existing data do not identify the bases for the chronic recidivism of some deinstitutionalized mentally ill. Is it the result of gaps in current knowledge regarding requisite community mental health services, is it the product of inadequate resources, or are there different reasons for the failures in divergent subpopulations?

The service system developed in the Massachusetts Department of Mental Health's region I under the terms of the Northampton Consent Decree (30, 31) has met virtually all of the requirements of a comprehensive system of community-based care (32). It thus offers an unprecedented opportunity to examine the correlates of successful and unsuccessful community tenure with the potentially confounding effects of resource inadequacies all but eliminated.

Clearly, the avoidance of hospitalization represents but one of the desired outcomes of the Northampton Consent Decree and of the deinstitutionalization process in general. There are those who would argue that it is a poor indicator of success, both for patients and the systems that serve them (33–35). Indeed, socialization, employment, and integration into community life may be much more important indices of success. However, brief community tenure and frequent hospitalizations thwart efforts to achieve these other goals. Examination of patients' characteristics and hospital utilization patterns is therefore an important first step in determining for whom funded deinstitutionalization, as represented by the Northampton Consent Decree, was most successful and for whom strategies for prolonged community tenure went unrealized.

## METHOD

Patients in residence at Northampton State Hospital on Dec. 7, 1978, were identified by using the year-end patient roster for June 30, 1978, and the hospital's admission and discharge log. Patient records were examined to obtain data on sociodemographic characteristics, primary and secondary *DSM-III* diagnoses, hospitalization history, legal status, the type of setting from which the patient had been referred on the index admission, dates of discharge and subsequent readmission (if any) after the index admission, program refer-

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The authors thank the staff of the medical records department of Northampton State Hospital for assistance with data collection and acknowledge the support and assistance provided by Aaron Lazare, M.D.

rals, and the number of hospitalizations at Northampton State Hospital. Data on patient deaths after discharge from the index admission were obtained from patient records and from computerized mortality data provided by the Massachusetts Department of Public Health.

Survival analysis (36) was used to examine the postdischarge community tenure of individuals discharged from the index admission to one of four classes of community placements, and failure rate regression (37) was used to identify significant predictors of community tenure. Logistic regression (38, 39) was applied to identify factors that predicted any readmission after discharge from the index hospitalization, and an ordinary least squares regression model was used to assess the effects of patient and setting characteristics on the number of admissions among the sample of patients with at least one postdecree admission.

## RESULTS

Data describing the demographic, diagnostic, hospitalization history, and prior residential characteristics of the sample as it appeared on Dec. 7, 1978, are summarized in tables 1 and 2. These data describe a population similar to that depicted in other studies of state hospital inpatient populations that were conducted in the 1970s (40, 41).

### *Discharge Patterns*

As of Dec. 7, 1986, the index admission had ended for all but three of the 368 patients in the identified sample. (Of these three, one was discharged in October 1988 after 11 years at Northampton State Hospital, one was discharged late in December 1986 after 24 years, and one was discharged in December 1988 after four decades at Northampton State Hospital.) Not all patients were discharged to the community, however. Twenty-two (6.0%) died while hospitalized, 16 (4.3%) were returned to court after evaluation for competency, and 44 (12.0%) were transferred to alternative mental health or medical inpatient settings, such as Veterans Administration hospitals. The discharge destinations for 16 patients (4.3%) were not recorded in such a way that they could be classified, and they were included in the category "other."

Seventy-three percent of the sample (N=270) were discharged to a noninstitutional community setting. This occurred over a period of 8 years, as patients became clinically ready for placement and as programs suited to their particular needs became available. These settings included home, living either independently or with family or friends (26.3%, N=71); nursing or convalescent homes (13.3%, N=36); residential programs for the mentally retarded (11.5%, N=31); and residential programs for the mentally ill (48.9%, N=132), including group homes, staffed apartments, and the community support program.

**TABLE 1. Characteristics in 1978 of Northampton State Hospital (Massachusetts) Patients, All of Whom Were Discharged by 1988 (N=368)**

| Characteristic | N | % |
|---|---|---|
| Sex | | |
| Male | 212 | 57.6 |
| Female | 156 | 42.4 |
| Age (years)[a] | | |
| <20 | 9 | 2.4 |
| 20–29 | 68 | 18.8 |
| 30–39 | 71 | 19.6 |
| 40–49 | 57 | 15.7 |
| 50–59 | 50 | 13.8 |
| 60–75 | 91 | 25.1 |
| ≥76 | 21 | 5.8 |
| Race[a] | | |
| White | 333 | 92.7 |
| Black | 22 | 6.1 |
| Hispanic | 4 | 1.1 |
| Education (years)[a] | | |
| 0 | 25 | 8.1 |
| 1–8 | 76 | 24.6 |
| 9–12 | 155 | 50.3 |
| 13–16 | 47 | 15.2 |
| 17–20 | 4 | 1.3 |
| Marital status[a] | | |
| Married | 36 | 9.9 |
| Never married | 261 | 70.9 |
| Widowed, separated, or divorced | 64 | 17.7 |
| Primary diagnosis | | |
| Organic | 58 | 15.8 |
| Schizophrenia, psychosis | 216 | 58.7 |
| Affective disorder | 24 | 6.5 |
| Mental retardation | 37 | 10.1 |
| Other | 33 | 9.0 |
| Legal status | | |
| Voluntary | 119 | 32.3 |
| Involuntary (civil) | 193 | 52.4 |
| Court evaluation | 37 | 10.0 |
| Prison referral | 2 | 0.5 |
| Other | 17 | 4.6 |
| Length of stay (index admission) | | |
| <1 month | 36 | 9.8 |
| 1–3 months | 73 | 19.8 |
| 4–6 months | 43 | 11.7 |
| 7–11 months | 26 | 7.1 |
| 1–2 years | 23 | 6.3 |
| 3–5 years | 48 | 13.0 |
| 6–10 years | 27 | 7.3 |
| 11–20 years | 33 | 9.0 |
| 21–30 years | 21 | 5.7 |
| 31+ years | 38 | 10.3 |

[a]Data missing for some patients.

### *Postdischarge Hospitalization*

A set of life table functions were developed for the 270 individuals discharged to community placements. Nine persons had unreliable discharge or readmission dates and were excluded from the analysis. Result are based on 261 cases. Life table functions take into account the timing with which individuals were withdrawn for other reasons (e.g., death) as well as terminated through readmission to Northampton State

**TABLE 2. History of Psychiatric Hospitalization as of 1978 of Northampton State Hospital (Massachusetts) Patients, All of Whom Were Discharged by 1988 (N=368)[a]**

| Number of Admissions | Cumulative Distribution (%) | | | | | |
|---|---|---|---|---|---|---|
| | Northampton Hospital[b] | Other State Hospitals | General and Private Hospitals[c] | State Forensic Hospitals | State Schools | Total[d] |
| 0 | 34.8 | 92.4 | 60.1 | 95.9 | 92.9 | 16.7 |
| 1 | 60.9 | 97.3 | 80.7 | 99.2 | 98.9 | 39.6 |
| 2 | 73.4 | 99.2 | 88.4 | 99.7 | 99.7 | 56.3 |
| 3 | 82.3 | 99.5 | 93.2 | 100.0 | 100.0 | 69.9 |
| 4 | 87.0 | 100.0 | 96.4 | | | 76.8 |
| 5 | 91.3 | | 97.3 | | | 82.1 |
| 6 | 94.3 | | 98.5 | | | 86.9 |
| 7 | 96.2 | | 99.1 | | | 91.1 |
| 8 | 97.8 | | 99.4 | | | 93.5 |
| 9 | 98.6 | | 99.7 | | | 94.9 |
| ≥10 | 100.0 | | 100.0 | | | 100.0 |

[a]Before index admission.
[b]Maximum=19 admissions.
[c]Maximum=11 admissions.
[d]Maximum=26 admissions.

Hospital. The survival function represents, for any time interval, the likelihood that a person at risk for readmission at the end of the previous interval will remain at risk (i.e., not be readmitted) at the end of the interval. This function indicates that 12 months after discharge, 72.7% of the sample (N=190) remained in the community and at risk for readmission. At 3 years, 52.1% of the sample (N=136) remained at risk for readmission.

The hazard function, which for any time interval represents the likelihood of readmission during that interval for individuals remaining at risk at the beginning of the interval, indicates that individuals were at greatest risk of readmission during the first month. As community tenure increased, the probability of readmission declined.

A failure rate regression model was used to assess the effects of patients' characteristics on community tenure. This technique derives coefficients for which positive values are indicative of higher likelihood of readmission at any point after discharge, and, hence, shorter community tenure; negative coefficients are associated with a lower likelihood of readmission at any point, and, thus, prolonged tenure. These coefficients can be mathematically transformed to provide estimates of differences in the likelihood of readmission at any point after discharge. The coefficients reflect the effect of a unit change in any patient characteristic variable and control for all other variables in the model (37).

Of the factors considered, two emerged as significant predictors—the number of prior admissions ($b=0.083$, asymptotic $t=2.707$, $p<0.05$) and age over 60 ($b=-1.387$, asymptotic $t=-2.980$, $p<0.05$). Transformation of these coefficients, as discussed earlier, indicates that, when other variables in the model are controlled, each prior admission increased the odds of readmission in any time interval by an average of 9%. In other words, patients who were recidivists in the period before the Northampton Consent Decree remained at higher risk for readmission. Conversely, persons over the age of 60 were, on average, only 25% as likely to be readmitted at any point as a person between 30 and 50 years old, who compromised the comparison group for the age variable.

*Readmissions Over the 8-Year Observation Period*

A substantial percentage (51%) of the individuals referred to one of the four settings described earlier were never readmitted to Northampton State Hospital. However, among those with at least one admission was a group of individuals with multiple admissions. The mean number±SD of readmissions for this group was 3.35±3.23.

Logistic regression was used to identify the effects of patient characteristics on the likelihood of readmission to Northampton State Hospital during the observation period. Age over 65 emerged as a significant negative predictor of the likelihood of readmission ($b=-0.913$, Wald statistic $[W]=-3.06$, $p<0.05$), while the number of prior admissions was found to be a positive predictor of readmission during the observation period ($b=0.206$, $W=2.134$, $p<0.05$).

An ordinary least squares regression model was developed for the number of admissions among the sample of patients with at least one postdecree admission. This model identified only one significant factor, discharge setting ($b=-2.03$, $t=-2.47$, $df=77$, $p<0.05$). Among patients with at least one admission, those placed in community residential programs for the mentally ill had significantly fewer admissions than did those living independently or with family (when patients' sociodemographic, diagnostic, and hospitalization history characteristics were controlled for). Nurs-

ing homes and residential programs for the mentally retarded showed no similar effect.

*Status 10 Years Later*

When records were reviewed in the winter of 1987–1988, only nine of the original 368 were inpatients at Northampton State Hospital at the time of their review. These nine displayed a rather heterogeneous pattern of hospitalization and community tenure. Five of the nine had had over five admissions since discharge from the index hospitalization. The fact that they were encountered at Northampton State Hospital at the time of their record review was thus a function not of extended hospitalization but of chronic recidivism. A sixth patient had had a community tenure of over 5 years, followed by rehospitalization for almost 20 months. This person has since been discharged. Another patient, discharged and readmitted within 3 months in 1980, subsequently remained hospitalized for more than 8 years. This individual was discharged in the fall of 1988. Only two patients displayed a pattern of brief community placement (1 month and 6 months) followed by indefinite rehospitalization and thus remained hospitalized in December 1989.

## DISCUSSION

Our examination of the impact of patient characteristics and discharge placement site on the likelihood of readmission, community tenure, and number of admissions in the resource-rich service environment developed under the aegis of the Northampton Consent Decree yielded relatively few significant predictors. Age was the most consistent demographic predictor of the several hospital utilization and community tenure variables. Specifically, age over 60 was significantly related to longer community tenure and a lower likelihood of readmission, and this points instead to a significant shift in the use of hospitalization after age 60. Since these relationships were examined in a multivariate framework that controlled for other factors described here, an elderly patient's community tenure was longer whether he or she was a short-stay, recently admitted patient or a long-stay patient hospitalized over 20 years who was placed in a nursing home or a specialized community residential program.

This finding is consistent with the observation made in the previous analysis regarding the virtual elimination of elderly persons from the patient population at Northampton State Hospital and their continued presence at Worcester State Hospital (30). If we were to identify who the "successes" of the Northampton Consent Decree effort were (in terms of their community tenure and hospital utilization patterns), it would clearly be this group. Creating community alternatives to state hospital care for geriatric psychiatric patients may represent the effort likely to yield the greatest return in terms of reducing the use of the state hospital.

The other most consistently significant predictor of community tenure and rehospitalization was prior hospitalization history. Patients with multiple admissions before the Northampton Consent Decree became the heaviest users of the hospital in the context of the decree's service system. Each hospitalization a patient had experienced before the index admission increased the likelihood of his or her ever being readmitted and the likelihood of readmission at any time after the index admission (thus reducing community tenure). Since the significance of this factor was established in a multivariate framework, its effect is independent of the effects of other potentially confounding factors, such as age and diagnosis.

Previous reviews of studies of rehospitalization among discharged state hospital patients have reported the number of prior admissions to be among the most consistently documented predictors of readmission (42, 43). From this standpoint, our finding a significant effect for this variable is not surprising. It is noteworthy, however, that most of the studies were carried out in the context of community-based service systems far less comprehensive and well-funded than that in region I. Our data indicate that many persons who have displayed a tendency toward frequent hospitalization will persist in that pattern even in the presence of such an intensive effort as that mounted under the Northampton Consent Decree.

The chronic mentally ill person who develops a "revolving-door" pattern of hospital utilization, a subtype found in virtually every catchment area in the United States, represents a category of patients whose needs were relatively poorly met by the comprehensive system of community-based care and treatment created by the Northampton Consent Decree, particularly in comparison to older patients. This population's needs must be specifically addressed through targeted interventions such as intensive case management (44–47) or involuntary community treatment (48–50) and through a service system plan that includes access to hospitalization. This reinforces the point that the state hospital or its equivalent will continue to play a prominent role even in a comprehensive system of community-based care and treatment, especially when that system focuses its efforts on residential placement, emergency services, and standard case management.

The state hospital recidivists in second-generation deinstitutionalization are a particularly interesting and challenging group. One of us (J.L.G.) has done a preliminary investigation of this population (43); a comprehensive evaluation of heavy users of the Northampton State Hospital is a focus of our ongoing investigation.

The underpinnings of the Northampton Consent Decree were perhaps undermined by a misperception of the nature of serious mental illness itself. For many individuals, chronic mental illness is a cyclical process, and its exacerbations may lead to the need for hospitalization even in adequately funded community service systems. The difficulties that the postdecree service system had in permanently sustaining many of region I's seriously

mentally ill patients in the community may be another demonstration that chronic mental illness has social, interpersonal, and biologic consequences previously inappropriately ascribed exclusively to institutionalism (51, 52).

Further, life in the least restrictive alternative, with its imputation of greater individual rights, includes greater choices about compliance with treatment and the right to fail. The effects of noncompliance with treatment, and perhaps refractoriness to treatment, have proven to be more malignant than anticipated (43). At the same time, life in the community places the mentally ill at risk for substance abuse and other forms of potentially self-injurious behaviors that are perilous for the general population but potentially disastrous when coupled with chronic mental illness (16). Finally, community life may require some of the chronic mentally ill with impaired social skills to adopt hazardous means of communicating wishes or needs for lower-intensity environments, as demonstrated by Geller in his study of communicative arson (53). Life in the community and the hazards of freedom may thwart the best efforts of service providers to stabilize some patients and prolong their community tenure.

If treatment in the least restrictive alternative appropriate to one's needs is the overarching, guiding principle of mental health policy, as it is in the Northampton Consent Decree, what actually can be achieved, even with adequate funding? The Northampton Consent Decree provides us with the opportunity to study the feasibility and the implications of responsibly pursuing this tenet. Follow-up questions to this study include examinations of quality of life issues, cost comparisons, calculations of actual versus imputed constraints on liberty, determinations of psychiatric and physical morbidity, and assessments of patient choice. The outcomes of the Northampton Consent Decree abound with policy implications. The lessons to be learned from this experiment in second-generation deinstitutionalization will surely have significance for the kinds of community services, inpatient facilities, and the interfaces between the two that will best serve future generations of the chronic mentally ill.

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# Avoiding Negligent Release: Contemporary Clinical and Risk Management Strategies

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*Mental health professionals often must decide whether to release a psychiatric patient who has been committed for treatment on the basis of being mentally ill and dangerous. This decision involves liability risks if the patient becomes violent after release. The author draws together several recommendations made in the literature regarding the careful development and implementation of hospital release procedures, including 1) special consultation at the policy development stage, 2) preemptive judgments regarding the adequacy of hospital policies in relation to the professional standard of care, and 3) the use of videotaped exit interviews with patients at the time of their release.*

(Am J Psychiatry 1990; 147:994–997)

The decision to release a psychiatric patient who has been involuntarily committed for treatment can be one of the most challenging and, at times, frightening decisions a mental health professional has to make. This is particularly true if the patient was originally committed on the basis of dangerousness to others (as opposed to grave disability, for example) because the decision to release at least implies a judgment, if not a prediction, by the hospital staff that the patient no longer poses a substantial threat to the safety of others. If the patient eventually harms someone after his or her release, the mental health professionals and hospital administrators responsible for the release decision may find themselves in court as defendants in a negligent release case brought by the victim or the victim's family.

It has been reported that negligent release cases occur less often than other types of psychiatric malpractice cases (1); however, this finding is probably based on the number of reported cases and may not reflect cases resolved by out-of-court settlement. Further, negligent release cases have resulted in some of the largest judgments of all psychiatric malpractice cases. In 1982, there were individual judgments of $10.1 million and $25 million in negligent release actions in New York and Alabama, respectively (1). A single negligent release case in Alabama in 1987 resulted in a judgment of $6.75 million against three hospital staff members. (The judgment was rendered in the unreported case of *Dale v. Griffin*. The judgment against the three mental health professionals was reversed in *Barnes v. Dale* [2].) Although negligent release actions predate the series of cases stemming from the *Tarasoff* decision (3), the various "duties" imposed on mental health professionals by *Tarasoff* and its progeny have broadened the base on which such tort claims may proceed (4–6).

In order to reach a judgment against defendant mental health professionals, a jury must find three things: first, that the defendant was negligent in making the decision to release; second, that the plaintiff was harmed; third, that the negligence was the proximate cause of the harm. For the defendant, the key to a successful defense lies in demonstrating that the release decision was not made negligently and/or that the release decision did not cause the harm.

The purpose of this paper is to describe clinical and risk management measures that clinicians can use to ensure that release decisions are made competently and carefully. I will draw on various ideas and recommendations that have appeared in the professional literature and that respond to three crucial issues that arise at trial: 1) how to demonstrate to the jury that the release decision was made diligently, not negligently, 2) how to offer objective evidence on the issue of whether the release decision was made in accordance with the prevailing standard of care of the profession, and 3) how to project a positive picture of the released patient to the jury.

## DEMONSTRATING DILIGENCE IN RELEASE DECISIONS

Obviously, decisions regarding the release of involuntarily committed patients should be governed by policy and procedure and should not be the outcome of individual, idiosyncratic actions. Perhaps less obviously, in developing its policies a hospital can take specific actions that enhance the quality of the release procedures themselves. These actions also place the

Received Oct. 11, 1989; revision received Feb. 12, 1990; accepted March 1, 1990. From the Taylor Hardin Secure Medical Facility. Address reprint requests to Dr. Poythress, Taylor Hardin Secure Medical Facility, 1301 River Rd., N.E., Tuscaloosa, AL 35404.

hospital in the position of being able to demonstrate special diligence in making release decisions.

*Special Policy Development*

One way to demonstrate diligence is to develop policies that govern release decision making in a special way. It is often the case that routine hospital policies are drafted by an individual staff member or an in-house committee and then reviewed and approved by the medical staff executive committee for implementation. For policies that govern release decision making, however, greater care can be demonstrated by having clinical staff confer with legal consultants in the policy drafting process (unpublished 1988 paper of J. Monahan). By selecting consultant personnel who have some experience and expertise in the important issues of release decision making, sound advice regarding substantive procedures can be obtained and diligence beyond the routine method for policy development can be demonstrated. Even in the face of an unfortunate outcome in a particular case, it can be argued that special care and consideration was given early on to the process of release decision making.

*Explicit Documentation of Violence Assessment*

Diligence can also be demonstrated by requiring the clinical staff, as part of its pre-release deliberations, to systematically develop and document information pertinent to its assessment of the patient's potential for violence. Most hospital records will have the usual documents, including a mental status examination, psychological evaluation, social history, progress notes, and so forth, available for review by the clinical staff at the point that release is being considered. Relatively few hospitals, I suspect, require staff systematically to cull from these various sources the information most relevant to judgments about the potential for violence. Without such a requirement, however, defendant clinicians are vulnerable to (possibly correct) claims that information pertinent to the assessment of potential violence scattered throughout the record was either missed or not meaningfully integrated by the clinical staff. If a specific document is in the record to show that particular attention was paid to an assessment of potential violence, then the staff will be less vulnerable to claims that the release decision was made unsystematically or exclusively on such clinical considerations as "the patient's clinical condition is stable," "patient has reached maximum hospital benefit," and so forth.

Marra et al. (7) offered the Dangerousness Assessment Sheet, which contains eight content areas for specific screening by staff involved in assessments of patients' potential for violence. Similarly, in an unpublished 1989 paper I described the violent behavior analysis required at one maximum security forensic hospital in Alabama for evaluating patients judged not guilty by reason of insanity who were candidates for release to the community. Given the state of the art of violence assessment and prediction (8, 9), there is no *one* way to compile and evaluate information pertinent to the potential for violence, and there may be differences of opinion among staff in different settings as to the variables to be assessed and the weights to be assigned to them. The important thing is that the staff be alerted to consider systematically the important issues and variables that have been identified in the professional literature as relevant to violence recidivism and that concrete documentation of the staff's action be in the patient's medical record. Apart from its value in promoting good, consistent clinical decision making, the evidentiary value of a concrete violence assessment document for convincingly demonstrating that special attention was given to the issue of potential for violence during release deliberations should not be underestimated.

*Hierarchical Review*

Release procedures should be written in such a way that the proposal to release is reviewable, on either an elective or mandatory basis, by senior consulting staff or a review committee (10). The policy might provide a mandatory review for patients in an actual (i.e., extensive violence history) or perceived (i.e., not guilty by reason of insanity) status of relatively higher risk and optional review for other involuntarily committed patients. The purpose of the independent review is not to dilute the responsibility for the decision but, rather, to incorporate the time-honored mechanism of a second opinion for important clinical decisions (11). Use of a mechanism for second opinions also highlights the staff's awareness of the importance of release decisions and supports the assertion that such decisions are made diligently.

## MEETING THE PROFESSIONAL STANDARD OF CARE CRITERION

In pressing their claim of negligence by defendant clinicians, plaintiffs will focus both on the release decision itself and the procedure used to arrive at it. Whatever information was gathered by defendants to inform the release decision, plaintiffs will claim that it was insufficient in depth or scope. Any information not sought or obtained by the clinicians will be portrayed to the jury as absolutely crucial or essential to the release decision. Armed with hindsight regarding the unfortunate result of the release decision, plaintiffs will argue further that the patient's violence was foreseeable and predictable and that the decision to release was itself an act of negligence.

In responding to these challenges, defendant clinicians will have to explain the rationales for their procedures and for the decision ultimately reached. It is important to note that in previous negligent release cases, the appellate courts have repeatedly placed em-

phasis on procedure rather than outcome as the locus of inquiry for psychiatric negligence:

> Negligence cannot be imputed to the hospital merely because of a mistake . . . . Error and uncertainty considered alone must often be accepted without labelling them negligence . . . a therapist who uses the proper psychiatric procedures is not negligent even if his diagnosis may have been incorrect. (12)

Whether or not the jury is impressed with evidence that emphasizes procedure over results, a careful record should be developed along these lines in anticipation of the appeal of an adverse decision.

The judgment of negligence will ultimately hinge on whether the staff met the profession's standard of care in making the decision to release. To date, none of the major mental health professional organizations (e.g., APA and the American Psychological Association) has issued specific standards for making release decisions. Thus, in actual negligent release tort cases the criterion for the standard of care is given substance by the testimony of expert witnesses hired by the plaintiffs and the defendants.

A risk management procedure that I described more extensively elsewhere (13) is to have consultant mental health professionals prejudge the hospital's policies and procedures regarding release decisions against the standard of care at the time the policies are developed. After working drafts of the policies and procedures have been completed, the hospital asks a group of mental health professionals (preferably including some known to have expertise in the area of violence assessment and/or release decision making) to review the draft and give their opinion as to whether the proposed policies and procedures meet what they consider to be the professional standard of care.

At least two potential benefits accrue from applying this procedure at the stage of policy development. First, the consultants can be asked to give specific feedback regarding any aspect of the procedures that they think is not up to the standard of care. This feedback can then be used to bring the policies up to standards. Second, this review process itself constitutes additional evidence of diligence in policy development; the process can be described to a jury in court to demonstrate further care given to the development of policies governing release decision making.

Additional uses for this judgment procedure can come into play in court. First, the expert consultants themselves can be called in as witnesses to testify as to their appraisal of the hospital's release procedures with respect to the professional standard of care. Because their judgments will have been formed at the stage of policy development and not in the heat of litigation, these witnesses should be less vulnerable to the usual accusations by plaintiff's attorneys of being "hired guns" brought in to justify or excuse the defendants' negligent practices. Further, if the group of expert consultants is of any substantial size, defendants can argue that, in addition to their relative neutrality with respect to the current litigation, the collective appraisals of these experts represent broader and more representative opinions of the profession than those of the (usually) one or two experts hired by the plaintiffs. Even if the expert consultants themselves are not brought in as witnesses, the defense may introduce the written correspondence with these consultants to demonstrate both the diligence of the procedure development and the results of the experts' appraisals.

## PROJECTING A POSITIVE IMAGE OF THE RELEASED PATIENT

A third substantial problem in negligent release cases is that of projecting a positive image of the released patient to the jury. There are, of course, substantial differences across cases in the clinical and behavioral histories of released patients. In most instances, the plaintiff's attorneys will be able to find in the records some documentation of behavioral incidents (e.g., incidents leading to commitment and inpatient behavior leading to seclusion or restraint) as well as psychiatric diagnoses and labels (e.g., schizophrenic, psychotic) that are at least misunderstood if not also frightening to many lay persons. These carefully selected incidents, anecdotes, and labels will be weaved together by the plaintiff's attorney in such a fashion as to impel the jury to conclude that the defendants released a "raving madman" or a "walking time bomb" to the community.

In one case, the plaintiff's attorney brought a large easel into the courtroom and placed it about three feet from the jury box. Mounted on the easel was a large, white piece of heavy construction cardboard. Professionally printed on the cardboard in large black letters, easily read from the farthest corner of the jury box, was a chronology of the released patient's worst sins as gleaned by the plaintiff's attorney from the records: "1978—arrested for drunk and disorderly conduct," "1980—struck wife with fist in a family dispute," "1981—reported outside alcoholics recovery center threatening to kill someone if not admitted," and so forth. This visual display of the patient's worst moments remained in front of the jury box throughout the trial as a constant reminder of the kinds of evil and unpleasant things that the patient had been capable of doing in his worst moments.

Defendants, of course, have the opportunity to testify about the patient's finer points and to affirm that, whatever he or she may have done previously, the patient was in moderate to good remission at the time of release. In the face of the known violence committed by the patient after release, the defendants' oral assurances are probably difficult for many jury members to accept. Without hard evidence, I suspect that this is particularly true when there is a large, concrete, visible reminder (e.g., an easel) of the patient's evil character that has been constructed by the plaintiff's attorney. As the defendant witnesses' words fade away and the next

matters are dealt with, the visual reminder of the patient's worst moments remains. Each glance at the easel, which is so situated that a glance is hardly avoidable, constitutes a reminder to the jury member of the patient's bad character. If there is any truth to the claims that repetition facilitates learning, jurors in this situation learn that the defendants released a terrible person from the hospital.

I recommend that hospitals make provisions for videotaped exit interviews to be conducted by skilled clinical staff at or near the release date. In other contexts, attorneys have found videotaping of clients to be a potentially effective method for refuting claims arising later that their client was mentally incompetent at the time that some important personal or legal decision was made—e.g., writing or signing a will. I suggest that clinicians can use the same device to preserve a live, colorful, dynamic record of the patient as he or she was when released. By carefully structuring the interview, many of the issues of concern in release decision making and in the management of violent patients can be addressed. These include patients' having any current or recent thoughts, feelings, or intentions of being aggressive toward anyone else; patients' personal plans; their awareness of their proposed living conditions; and their awareness of and attitude toward medications and aftercare plans. One hopes that patients will give the "right" answers most of the time. Even when they do not, however, the clinician may respond on tape by acknowledging some concern about a particular response by the patient and by mentioning the clinical feature or aftercare plan that is intended to address this concern.

Mental health professionals and attorneys are both accustomed to doing their jobs with words. When it comes to impression formation, however, the power of the visual medium should not be underestimated. Just as a concrete document called "Dangerousness Assessment Sheet" can erase any doubt that the clinicians systematically addressed the issue of potential for violence, a videotape of the patient's exit interview may go a long way toward shaping the jury's view of the patient as he or she appeared at the time of release.

## CONCLUSIONS

Mental health professionals responsible for the treatment of mentally ill persons who are potentially violent cannot avoid the anxiety-arousing decision to release patients whose clinical conditions and behavior have improved to the point that discharge from the hospital is warranted. Anxiety about the possibility of subsequent aggressive behavior and the attendant liability risks for the clinician can be minimized, however, by implementing careful release procedures that attend not only to competent clinical practices but to risk management issues as well. The end results may include reduced job-related stress and increased morale for clinicians as well as reduced risk of unnecessary and costly litigation for the hospital administrators involved in these decisions.

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# Drug Use and Life Style Among College Undergraduates in 1989: A Comparison With 1969 and 1978

Harrison G. Pope, Jr., M.D., Martin Ionescu-Pioggia, Ph.D., Harlyn G. Aizley, M.Ed., and Deep K. Varma, B.A.

*The authors conducted anonymous questionnaire studies of drug use and life style among college seniors at the same institution in 1969, 1978, and 1989. The 1989 group of students reported strikingly lower frequencies of virtually all forms of drug use than their counterparts in 1969 and 1978. As in 1969 and 1978, the drug users among the 1989 group were indistinguishable from nonusers in grades, athletic activities, other college activities, and feelings of alienation. Only visits to a psychiatrist and sexual activity distinguished users from nonusers.*

(Am J Psychiatry 1990; 147:998–1001)

Many studies over the last 20 years have investigated drug use on college campuses, with widely varying results. Not only have these studies varied in their focus and methods, but most have examined the attributes of a single college population at a single time. Only a few studies (1–5) have examined trends over time at a given institution; most of these have shown large differences in the rates of various forms of drug use at different times. For example, we distributed anonymous questionnaires to members of the senior class at the same institution in 1969 (1) and again in 1978 (2). The 1969 and 1978 students reported roughly similar rates of having ever used alcohol, marijuana, amphetamines, and hallucinogens; however, the students in the 1978 study group reported much higher lifetime rates of cocaine use and higher rates of weekly marijuana use than their 1969 counterparts.

In an attempt to provide data on long-term trends in college drug use, in 1989 we again distributed anonymous questionnaires to seniors at the same college we had studied previously. The results thus provide a 20-year view, from 1969 to 1989, of trends in drug use at the same college.

## METHOD

The methods used in 1989 were virtually identical to those of the two previous studies (1, 2). Anonymous questionnaires were distributed to college seniors at registration in February 1989. Of 1,779 seniors, approximately 430 accepted a questionnaire, and 369 (approximately 86%) of these students deposited completed questionnaires in the sealed box provided. The complete questionnaire was published with our first study (1). The questionnaire was the same as that used in the previous years with the following exceptions: the drug use categories of methaqualone, tetrahydrocannabinol (THC), amyl nitrite, phencyclidine (PCP), and nitrous oxide, all of which were used in 1978, were deleted in 1989. However, students were asked a question regarding other drugs used; here they could write in any of these drug categories if they wanted to. Questions on Scholastic Aptitude Test scores and career plans were also deleted from the 1989 questionnaire, and a question on anabolic steroid use, not present in previous years, was added. Finally, through an oversight, the 1989 questionnaire did not contain a question on the gender of the respondent. This omission required that all results be presented for both sexes combined; in practice, however, this did not hinder most comparisons between the 1989 results and those of earlier years.

As in previous years, the representative nature of the sample was tested by comparing its characteristics against the college's own records for the entire senior class on two items: residence (on-campus versus off-campus) and grades. The proportion of questionnaire respondents reporting residence off campus (10.1%) agreed closely with the college's data for the senior class as a whole (10.8%). The mean grade-point averages reported by questionnaire respondents for their freshman, sophomore, and junior years were also not

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The authors thank Burroughs Wellcome Co. for research support and Ross N. Raymond and Mark Huber for assistance with data analysis.

significantly different from those of the rest of the students in the class of 1989 in each of these three years.

As in 1969 and 1978, three comparisons were performed. First, nonusers (those who reported never using an illicit drug) were compared with all users (those who had used any illicit drug one or more times). Second, nonusers were compared with hallucinogen users (those who had used LSD or another hallucinogen at least once). Third, nonusers were compared with long-term users (those who had first used an illicit drug at least 3 years before the study was conducted). Further details on these categories, which are identical to those used in the previous study years, are presented in the earlier reports (1, 2).

Groups were compared by using Fisher's exact test for two-by-two comparisons, the exact permutation test program of Halvorsen and Pagano (6) for larger two-by-N comparisons, the t test for comparisons of normally distributed continuous variables, and the Wilcoxon rank-sum test for variables that did not prove to be normally distributed.

## RESULTS

### *Rates of Drug Use*

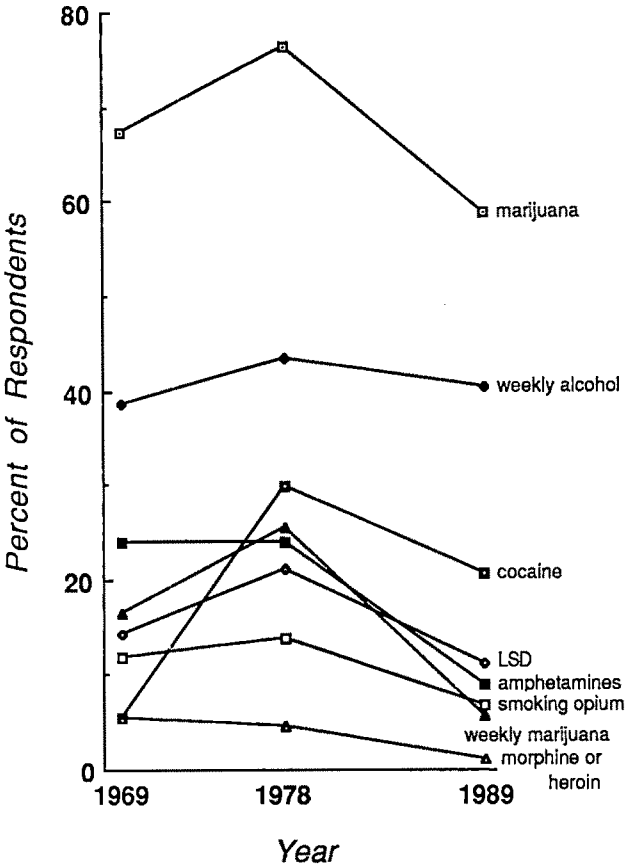
Figure 1 compares the rates of various forms of drug use across the 20-year period spanned by this study and its two predecessors. Note that figure 1 contains both incidence rates (having ever used a given drug at any time in one's life) and two prevalence rates (current use of alcohol and marijuana once a week or more). The incidence of alcohol use (having ever used alcohol) is not shown in the figure because it has remained stable at nearly 100% (96% in 1969, 97% in 1978, and 97% in 1989). However, the use of virtually all other drugs decreased in 1989 from 1969 and 1978 levels. Perhaps most striking is weekly marijuana use, reported by only 5.7% of the 1989 group of students, compared with 26% of the 1978 group of students. Even use of cocaine, which rose dramatically between 1969 and 1978, appeared to have declined in 1989 from its 1978 peak. Only 1.4% of the 1989 group of respondents reported use of anabolic steroids. Figures from previous study years were not available for this drug category.

### *Attributes of Drug Users*

As in the 1978 study, no significant differences were found between nonusers and users, between nonusers and hallucinogen users, and between nonusers and long-term users on most of the indexes assessed in 1989. These included grade-point averages for freshman, sophomore, and junior years; participation in college athletic activities, clubs, and political organizations; and feelings of "alienation from American society." Indeed, the question on alienation, which produced robust differences between drug users and nonusers in the 1969 study, produced few positive responses among either users or nonusers 20 years later. Of the total group of respondents in 1969, only 10.5% said that they were definitely not alienated; among the 1989 respondents, the figure was 42.7%—a highly significant difference ($p<0.001$).

Two factors continued to distinguish drug users from nonusers in the same way that they had in the previous study years: visits to a psychiatrist and sexual activity. The results of these comparisons are shown in tables 1 and 2. On visits to a psychiatrist, the absolute frequencies and the differences between nonusers and

**FIGURE 1. 1969, 1978, and 1989 Groups of College Seniors Reporting Use of Various Drugs[a]**




[a]All rates represent the percent of students who had ever used a given drug in their lifetime, except for the categories of weekly marijuana and weekly alcohol, which represent the percent of students reporting current weekly use of these substances. Cocaine, morphine, and heroin were combined as one category in 1969; therefore, rates for these drugs cannot be computed separately. The significance of the difference in rates of morphine and heroin use in 1989 versus 1969 also cannot be calculated. The differences between rates in 1989 and 1978 for all drug categories except morphine ($p=0.004$) were significant at $p<0.001$; the difference was not significant for weekly alcohol use. The differences between rates of drug use in 1989 and 1969 were significant for weekly marijuana, amphetamine, and cocaine ($p<0.001$), for marijuana ($p=0.01$), and for smoking opium ($p=0.02$) and nonsignificant for weekly alcohol and LSD.

**TABLE 1. Drug Use and Visits Made to Psychiatrists by 1989 Group of 356 College Seniors[a]**

| Number of Visits to Psychiatrists | Nonusers (N=148) | | All Users (N=208) | | Hallucinogen Users[b] (N=59) | | Long-Term Users[b] (N=154) | |
|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % |
| One or none | 136 | 91.9 | 169 | 81.3 | 45 | 76.3 | 125 | 81.2 |
| A few or more[c] | 12 | 8.1 | 39 | 18.8 | 14 | 23.7 | 29 | 18.8 |

[a]Only 356 of the 369 students gave complete responses for these questions.
[b]Some of the hallucinogen users were also long-term users; long-term users had first used an illicit drug at least 3 years before the survey was conducted.
[c]Significantly fewer nonusers than all users ($p<0.009$), hallucinogen users ($p<0.007$), and long-term users ($p<0.01$) had visited a psychiatrist a few times or more (Fisher's exact test for two-by-two tables).

**TABLE 2. Drug Use and Heterosexual Activity of 1989 Group of 348 College Seniors[a]**

| Heterosexual Activity | Nonusers (N=144) | | All Users (N=204) | | Hallucinogen Users[b] (N=58) | | Long-Term Users[b] (N=149) | |
|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % |
| Had not had intercourse | 69 | 47.9 | 29 | 14.2 | 4 | 6.9 | 15 | 10.1 |
| Had had intercourse with at least one partner[c] | 75 | 52.1 | 175 | 85.8 | 54 | 93.1 | 134 | 89.9 |

[a]Only 348 of the 369 students gave complete responses for these questions.
[b]Some of the hallucinogen users were also long-term users; long-term users had first used an illicit drug at least 3 years before the survey was conducted.
[c]Significantly fewer nonusers than all users, hallucinogen users, and long-term users had had intercourse with at least one partner ($p<0.001$, Fisher's exact test for two-by-two tables).

the three user categories were very similar to those observed in the previous study years. As in the previous years, however, the differences between nonusers and users on this variable did not appear attributable to drug use itself: of 52 users who had seen a psychiatrist at least once, only one said that the problem was due to drug use, and three others felt that the problem was possibly due to drug use.

The respondents' heterosexual activity is summarized in table 2. Although the 1989 group of students reported markedly lower rates of drug use than the 1969 and 1978 groups of students, the overall rates of heterosexual activity were similar in all three study years. In 1969, 70% of all respondents reported having had intercourse with at least one partner; about one-third of these (21% of the total group) reported having had intercourse with many partners. In 1978 these two figures were 78% and 28%, respectively; in 1989, they were 72% (N=250) and 20% (N=69) (348 subjects answered this question). In 1989, as in the previous years, all categories of drug users reported significantly more heterosexual experience than did nonusers.

Note that the results in table 2 are shown for both sexes combined because the 1989 questionnaire did not include a question on the gender of the respondent. In both the 1969 and 1978 studies, however, no significant difference was found between men and women in any of the drug use categories in the fraction who reported heterosexual intercourse with at least one partner. Therefore, it appears unlikely that the combined figures presented for the drug users in 1989 are masking any large difference in frequencies between the sexes.

## DISCUSSION

Our three anonymous questionnaire studies of drug use and life style among college seniors at the same institution in 1969, 1978, and 1989, performed with virtually identical methods, provide a 20-year perspective on the evolution of drug use at one college. The most striking finding of the 1989 study was that most forms of illicit drug use, which had risen in frequency between 1969 and 1978, had declined substantially by 1989. This trend is particularly illustrated by the frequency of weekly marijuana use, which rose from 16% in 1969 to 26% in 1978 and then dropped to only 6% in 1989.

It is difficult to compare these trends with those observed in other studies of college students because no other study, to our knowledge, has spanned a comparable time period. Perhaps the most similar study is that of Patterson et al. (5), who compared drug use patterns at a small Southern university in 1972 and 1986. These authors also found a decline in use of amphetamine and LSD between the two years, but they found little change in marijuana use and a marked rise in cocaine use; lifetime use of cocaine rose from 10% in 1972 to 40% in 1986. The latter figures may

differ from ours either because of the different years chosen or because of the different study site.

Another study with a similar method is that of Dezelsky et al. (3), who tracked drug use on five college campuses from 1970 to 1980. These authors found a rise in frequency of use of marijuana, cocaine, and amphetamines from 1970 to 1980 on most campuses —a finding that matches closely our findings in 1969 and 1978. Unfortunately, to our knowledge, Dezelsky et al. have not published data from any time after 1980, so that comparison with our 1989 figures is not possible.

Is the recent decline in drug use recorded in our study real or an artifact of methodology? The latter seems unlikely because a virtually identical method was used in all three study years. Any tendency to overestimate or underestimate drug use would likely have applied equally in all 3 years and thus would probably have had little effect on comparisons among years. Admittedly, the response rate in 1989 was lower than it was in 1969 and 1978, but this appeared to be due to the fact that more individuals were competing for students' attention at registration in 1989 than in earlier years, so that students were more difficult to recruit for the questionnaire. Comparing the college's statistics for the entire senior class with the respondents' answers to questions about their grades and about on-campus versus off-campus housing, we found that the 1989 group of students, although providing a lower response rate, were representative of the entire senior class.

Is it possible that lower drug use rates in 1989 reflected a change in the college's admissions policy? It might be speculated, for example, that admissions officers, apprehensive about high rates of student drug use or other deviant behavior, might have selected more conservative students in recent years. Although such selection is certainly possible, the data would seem inconsistent with this hypothesis. For example, the 1989 group of students reported virtually the same levels of sexual activity, including the same frequency of intercourse with many partners, as their earlier counterparts, and 148 (40.3%) of the 367 subjects who answered this question drank alcohol at least once a week, a figure comparable to the 38% and 43.5% rates in 1969 and 1978, respectively. Therefore, the 1989 group of students seemed equally involved in pleasurable activities other than illicit drug use; it was only their illicit drug use that declined. These observations would argue against major selection effects in the college admissions process.

Finally, the students who reported illicit drug use, although there were fewer of them than in 1969 and 1978, appeared little different from their nonuser counterparts on most measures of academic performance, college activities, and life style. As in 1978, only visits to a psychiatrist and sexual activity distinguished users from nonusers, and neither of these variables appeared to be related to drug use in a direct cause-and-effect way. It seems more likely, as it did in 1969 and 1978, that differences in attitudes and values of drug users rather than the drug use itself were responsible for these differences.

Although these findings are optimistic, it would be premature to conclude that college drug use is uniformly declining or that college drug users are consistently similar to nonusers in their life styles. Further longitudinal studies—particularly follow-ups at colleges last studied 5–10 years ago—would be most helpful to test the generalizability of our findings.

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# Substance Use in Borderline Personality Disorder

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*The authors investigated the prevalence of substance abuse in 137 inpatients with* DSM-III *borderline personality disorder. Ninety-two (67%) of these patients were given* DSM-III *substance use disorder diagnoses. The most frequently used substances were alcohol and sedative-hypnotics. When substance abuse was not used as a diagnostic criterion for borderline personality disorder, 32 (23%) of the 137 patients no longer met borderline criteria. These patients differed significantly from the rest of the patients in severity and course of illness. These data suggest that there might be a subgroup of borderline patients for whom substance use plays a primary role in the development of borderline psychopathology.*

(Am J Psychiatry 1990; 147:1002–1007)

Although illicit substance use is clinically recognized as common in borderline personality disorder and is often a major obstacle to effective psychotherapy, little empirical research has focused on the comorbidity of substance abuse and borderline personality disorder. The reported prevalences of comorbid substance abuse in borderline personality disorder range from 11% to 69% (1–5), but the criteria for substance use disorders in these studies were generally not well defined. Little is known about substance use patterns and preferences in borderline personality disorder, although Akiskal et al. (1) reported that most of the outpatients with *DSM-III* borderline personality disorder whom they studied preferred sedative-hypnotics or alcohol. There is some evidence that substance abuse in borderline personality disorder increases the risk for serious self-destructive behavior (6–8), but the relationship of substance use to borderline psychopathology has not been well studied. Some investigators have speculated that personality psychopathology may be a direct manifestation of substance abuse rather than substance abuse merely being one symptom of personality disorder (9), but this hypothesis has not been examined in borderline personality disorder.

In this study, we systematically documented rates and types of *DSM-III* substance use disorders in a large and diversified sample of inpatients with *DSM-III* borderline personality disorder in an acute general psychiatric hospital. We examined the role of substance use in the natural history, phenomenology, and diagnosis of borderline personality disorder.

## METHOD

This study was conducted as part of a larger investigation of comorbidity in borderline personality disorder. A sample of 180 patients with borderline personality disorder was selected by reviewing the charts of consecutive admissions (from December 1981 through February 1984) between the ages of 18 and 45 at the Payne Whitney Clinic and The New York Hospital-Westchester Division who were given a discharge diagnosis of borderline personality disorder by treating clinicians. Those who also met *DSM-III* criteria for borderline personality disorder by chart review were entered into the sample. The chart review diagnosis of borderline personality disorder required documentation that five of the eight *DSM-III* criteria were characteristic of the patient's long-term functioning before the index admission. In no case did we infer that a symptom or behavior had been present on a continuing basis unless this information was directly documented in the chart. All charts were further reviewed with a 76-item checklist and the *DSM-III* item sets to obtain demographic, diagnostic, and treatment history data. Interrater reliabilities for the diagnostic categories were equivalent to those reported in studies using prospective clinical interviews. The method of this chart review has been described in more detail elsewhere (10).

For the current study, 137 of the 180 original charts were re-reviewed to obtain comprehensive substance use data. Subjects from The New York Hospital-Westchester Division (N=41) were excluded from the present sample for logistical reasons, and two charts from the original Payne Whitney Clinic sample were unavailable for re-review. Charts were restudied with a

Presented at the 142nd annual meeting of the American Psychiatric Association, San Francisco, May 6–11, 1989. Received Aug. 18, 1989; revision received Dec. 13, 1989; accepted Jan. 25, 1990. From the Department of Psychiatry, The New York Hospital-Cornell University Medical Center. Address reprint requests to Dr. Dulit, Department of Psychiatry, The New York Hospital-Cornell University Medical Center, 525 East 68th St., New York, NY 10021.

Supported in part by an American Suicide Foundation Award (Dr. Dulit).

checklist to make current *DSM-III* substance abuse or dependence diagnoses in nine classes of psychoactive drugs: alcohol, sedative-hypnotics or anxiolytics, opioids, cocaine, amphetamines or similarly acting sympathomimetics (stimulants), hallucinogens, phencyclidine (PCP), cannabis, and inhalants. The essential feature of *DSM-III* substance abuse is a pattern of pathological use for at least 1 month that causes substantial impairment in social and occupational functioning. The essential feature of *DSM-III* substance dependence is either tolerance or withdrawal. For alcohol and cannabis dependence a pattern of pathological use or impairment in social or occupational functioning is also required. In no case did we presume that substance use existed at the time of index admission if only a past history was documented.

The review of charts for the purpose of assigning *DSM-III* substance use diagnoses was comprehensive and included the admission history, mental status examination, physical examination, progress notes, nursing and social work notes, and toxicology reports. To establish diagnostic reliability for the substance use chart review, 15 randomly selected records were reviewed blindly by two raters (R.A.D. and M.R.F.). The kappa values for *DSM-III* substance use disorder categories were as follows: alcohol, 0.85; sedative-hypnotics, 0.82; opioids, 1.00; cocaine, 0.85; stimulants, 1.00; and cannabis, 0.86. We were unable to assess interrater reliability for two low-frequency categories (hallucinogens and PCP). None of the patients used inhalants.

To support the validity of our chart review method to study substance use in borderline personality disorder, 13 of the patients whose charts had been reviewed were randomly selected and contacted by telephone. After providing informed consent, these former patients received a semistructured substance use interview (available on request from R.A.D.) to assess *DSM-III* substance use disorders at the time of their index admission. The rater who administered these interviews was blind to all chart review data. According to McNemar's test, there was no significant difference between chart review and interview diagnoses for the *DSM-III* substance use disorder category for these 13 patients. There was complete concordance on 12 patients: six were classified as non-substance-users and six as substance users both by chart review and interview. One subject was defined by chart review as a nonuser but was assessed by the interviewer as having three *DSM-III* substance use diagnoses.

Group comparisons for the entire sample were assessed with one-way analysis of variance (ANOVA) for continuous variables. Categorical variables were analyzed with the chi-square analysis, with Yates's correction when appropriate. For both continuous and categorical variables, we conducted three-way comparisons, and if the significance level was less than 0.05, we computed follow-up pairwise tests of significance.

This study used *DSM-III* rather than *DSM-III-R* diagnostic criteria. Only minimal changes were made in the diagnostic criteria for borderline personality disorder in *DSM-III-R*, and these would not have changed the diagnoses of any of the subjects in our study sample. The changes from *DSM-III* to *DSM-III-R* criteria for substance use disorders were major and remain controversial. Revisions broadened the definition of "dependence" by focusing more attention on loss of control of substance use and placing less emphasis on physical tolerance and withdrawal. These changes do not affect the conclusions of our study because we grouped subjects with abuse and dependence diagnoses together for the purposes of statistical analysis. It should be noted that nearly all subjects in our sample who met *DSM-III* criteria for substance abuse would also meet criteria for *DSM-III-R* psychoactive substance dependence.

**TABLE 1. *DSM-III* Substance Use Disorder in 137 Inpatients With *DSM-III* Borderline Personality Disorder**

| Substance Use Diagnosis | Patients With Substance Use Diagnosis | | Percent of Total Substance Use Diagnoses (N=228) |
|---|---|---|---|
| | N | % | |
| Alcohol abuse or dependence | 67 | 48.9 | 29.4 |
| Abuse | 46 | 33.6 | 20.2 |
| Dependence | 21 | 15.3 | 9.2 |
| Sedative-hypnotic abuse or dependence | 64 | 46.7 | 28.1 |
| Abuse | 40 | 29.2 | 17.5 |
| Dependence | 24 | 17.5 | 10.5 |
| Cannabis abuse | 33 | 24.1 | 14.5 |
| Cocaine abuse | 22 | 16.1 | 9.6 |
| Opioid abuse or dependence | 20 | 14.6 | 8.8 |
| Abuse | 13 | 9.5 | 5.7 |
| Dependence | 7 | 5.1 | 3.1 |
| Stimulant abuse or dependence | 16 | 11.7 | 7.0 |
| Abuse | 15 | 10.9 | 6.6 |
| Dependence | 1 | 0.7 | 0.4 |
| Hallucinogen abuse | 5 | 3.6 | 2.2 |
| Phencyclidine abuse | 1 | 1.0 | 1.0 |
| Inhalant abuse | 0 | 0.0 | 0.0 |
| No substance use disorder | 45 | 32.8 | — |

## RESULTS

The 137 borderline inpatients were relatively young (mean±SD age=29.0±6.4 years), and most of them were women (80%, N=110), white (86%, N=118), and either single, separated, or divorced (87%, N=119). Most were from Hollingshead-Redlich social classes I, II, and III (80%, N=110).

Table 1 summarizes the substance use disorder diagnoses of the sample. Of the 137 borderline patients, 92 (67%) received a total of 228 *DSM-III* substance use disorder diagnoses. Seventy-seven percent (N=175) of the diagnoses were *DSM-III* substance abuse disorders and 23% (N=53) were *DSM-III* substance dependence disorders. Of the 92 substance users (patients with diagnoses of substance abuse or dependence), 73% used alcohol and 70% used sedative-hyp-

**TABLE 2. Treatment History of Inpatients With *DSM-III* Borderline Personality Disorder With and Without *DSM-III* Substance Use**

| | Patients With Substance Use Disorders | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Given Borderline Diagnosis After Exclusion of Substance Use (N=60) | | Not Given Borderline Diagnosis After Exclusion of Substance Use (N=32) | | Patients Without Substance Use Diagnoses (N=45) | | Total (N=137) | |
| Treatment History | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Age at index admission (years)[a] | 28.4 | 6.0 | 31.7 | 6.8 | 27.9 | 6.4 | 28.9 | 6.5 |
| Age at first outpatient treatment (years)[b] | 16.4 | 9.7 | 20.7 | 8.0 | 15.1 | 8.6 | 17.1 | 9.1 |
| Age at first hospitalization (years)[c] | 22.2 | 6.8 | 27.3 | 6.6 | 23.2 | 8.1 | 23.7 | 7.5 |
| Number of outpatient treatment episodes | 3.9 | 3.6 | 3.9 | 2.8 | 4.0 | 3.3 | 3.9 | 3.3 |
| Number of hospitalizations[d] | 3.7 | 2.3 | 2.3 | 2.0 | 2.9 | 2.7 | 3.1 | 2.4 |

[a]F=3.85, df=2, 134, p<0.02. Substance users who were not given a borderline diagnosis after exclusion of substance use were older than substance users who were given the diagnosis after exclusion of substance use and non-substance-users (p<0.05, post hoc pairwise comparisons).
[b]F=3.72, df=2, 126, p<0.03. Substance users who were not given the borderline diagnosis after exclusion of substance use were older than non-substance-users (p<0.05, post hoc pairwise comparisons).
[c]F=4.85, df=2, 125, p<0.009. Substance users who were not given the borderline diagnosis after exclusion of substance use were older than substance users who were given the borderline diagnosis after exclusion of substance use and non-substance-users (p<0.05, post hoc pairwise comparisons).
[d]F=3.69, df=2, 134, p<0.03. Substance users who were not given the borderline diagnosis after exclusion of substance use had fewer hospitalizations than substance users who were given the borderline diagnosis after exclusion of substance use (p<0.05, post hoc pairwise comparisons).

notics; only 6% (N=6) did not use either, and 49% (N=45) used both. Other substances used included cannabis (36%), cocaine (24%), opioids (22%), amphetamines (stimulants) (17%), hallucinogens (5%), and PCP (1%). Twenty-seven percent (N=25) used only one substance, 35% (N=32) used two substances, and 38% (N=35) used three or more substances. (The percents in table 1 are based on N=137 rather than N=92.)

To explore the relationship between substance use and the diagnosis of borderline personality disorder, we subtracted the contribution of substance use as part of the first criterion for borderline personality disorder (impulsivity or unpredictability in at least two areas that are potentially self-damaging, such as spending, sex, gambling, substance use, shoplifting, overeating, and physically self-damaging acts) and reassessed the diagnosis of borderline personality disorder for all substance users in the sample. Of the 92 substance users, 32 (35% of the substance abusers and 23% of the total sample) no longer met *DSM-III* diagnostic criteria for borderline personality disorder. We then compared this subgroup with the remainder of the study sample: substance users who still met *DSM-III* diagnostic criteria for borderline personality disorder (N=60) and patients with borderline personality disorder who did not have substance abuse diagnoses (N=45). Significant differences were found among the subgroups on several measures (see tables 2 and 3).

Significant differences were found in the treatment histories of the three subgroups (see table 2). Substance users who failed to meet criteria for borderline personality disorder after exclusion of the substance use criterion were significantly older at the index admission and at their first psychiatric hospitalization than both of the other subgroups. The patients who failed to meet borderline criteria after exclusion of the substance use criterion were also significantly older at the age of first outpatient psychiatric treatment than nonuser patients and had significantly fewer psychiatric hospitalizations than patients who met criteria for borderline personality disorder irrespective of substance use. All other comparisons of demographic and treatment history variables among subgroups were nonsignificant. There were also no significant differences among subgroups in rates of comorbid affective disorders, psychotic disorders, organic disorders, and other personality disorders.

We then compared the three subgroups with respect to the frequency with which each of the *DSM-III* criteria for borderline personality disorder was met (see table 3) and again controlled for the contribution of substance use to the diagnosis of borderline personality disorder. Each of the patients who no longer met the criteria for borderline disorder after exclusion of substance use met four of the eight diagnostic criteria for *DSM-III* borderline personality disorder, whereas patients who still met the criteria for borderline disorder and patients who did not have substance use diagnoses met a mean±SD of 5.5±0.62 and 5.5±0.63 of the eight criteria, respectively. Patients who no longer met borderline criteria when substance use was not a criterion showed significant differences in four of the eight diagnostic criteria for borderline personality disorder. By definition, substance users who no longer met criteria for borderline personality disorder were significantly less likely to meet the criterion of impulsivity or unpredictability than either the patients who still met the criteria for borderline personality disorder or nonuser patients. They were also significantly less likely to meet the criterion of identity disturbance, manifested by uncertainty about several issues related

**TABLE 3. Inpatients With *DSM-III* Borderline Personality Disorder With and Without *DSM-III* Substance Use Who Met the Individual *DSM-III* Criteria for Borderline Personality Disorder**

| | Patients With Substance Use Disorders | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Given Borderline Diagnosis After Exclusion of Substance Use (N=60) | | Not Given Borderline Diagnosis After Exclusion of Substance Use (N=32) | | Patients Without Substance Use (N=45) | | Total (N=137) | |
| Criterion | N | % | N | % | N | % | N | % |
| Impulsivity or unpredictability[a] | 39 | 65 | 0 | 0 | 39 | 87 | 78 | 57 |
| Unstable relationships | 60 | 100 | 32 | 100 | 44 | 98 | 136 | 99 |
| Inappropriate anger | 49 | 82 | 27 | 84 | 38 | 84 | 114 | 83 |
| Identity disturbance[b] | 42 | 70 | 7 | 22 | 28 | 62 | 77 | 56 |
| Affective instability | 58 | 97 | 30 | 94 | 45 | 100 | 133 | 97 |
| Intolerance of being alone[c] | 6 | 10 | 1 | 3 | 10 | 22 | 17 | 12 |
| Physically self-damaging acts | 57 | 95 | 29 | 91 | 38 | 84 | 124 | 91 |
| Feelings of emptiness or boredom[d] | 18 | 30 | 2 | 6 | 5 | 11 | 25 | 18 |
| Minipsychotic episodes[e] | 28 | 47 | 4 | 13 | 22 | 49 | 54 | 39 |

[a] $\chi^2=63.9$, df=6, $p<0.00001$. Fewer substance users who were not given the borderline diagnosis after exclusion of substance use met this criterion than substance users who were given the borderline diagnosis after exclusion of substance use ($\chi^2=36.11$, df=1, $p<0.001$) and non-substance-users ($\chi^2=56.20$, df=1, $p<0.001$).

[b] $\chi^2=20.6$, df=2, $p<0.00001$. Fewer substance users who were not given the borderline diagnosis after exclusion of substance use met this criterion than substance users who were given the borderline diagnosis after exclusion of substance use ($\chi^2=19.42$, df=1, $p<0.001$) and non-substance-users ($\chi^2=12.28$, df=1, $p<0.001$).

[c] $\chi^2=6.8$, df=2, $p<0.03$. Fewer substance users who were not given the borderline diagnosis after exclusion of substance use met this criterion than non-substance-users ($\chi^2=7.24$, df=1, $p<0.01$, Yates's correction).

[d] $\chi^2=10.2$, df=2, $p<0.006$. Fewer substance users who were not given the borderline diagnosis after exclusion of substance use met this criterion than substance users who were given the borderline diagnosis after exclusion of substance use ($\chi^2=5.59$, df=1, $p<0.02$, Yates's correction).

[e] This was considered as a possible criterion for borderline personality in *DSM-III*. $\chi^2=14.7$, df=6, $p<0.02$. Fewer substance users who were not given the borderline diagnosis after exclusion of substance use met this criterion than substance users who were given the borderline diagnosis after exclusion of substance use ($\chi^2=10.74$, df=1, $p<0.01$) and non-substance-users ($\chi^2=11.07$, df=1, $p<0.001$).

to identity, than either of the other two groups, less likely to meet the criterion of intolerance of being alone than patients who were not substance users, and less likely to meet the criterion of chronic feelings of emptiness or boredom than patients who met criteria for borderline personality disorder regardless of substance use. All three subgroups were equally likely to meet the remaining four *DSM-III* criteria for borderline personality disorder: a pattern of unstable and intense interpersonal relationships; inappropriate, intense anger or lack of control of anger; affective instability; and physically self-damaging acts.

Since minipsychotic episodes have been considered by some as a possible criterion for borderline personality disorder (11), we assessed the frequency of a history of minipsychotic episodes for each subgroup. Patients who did not meet *DSM-III* criteria for borderline personality disorder after exclusion of substance use were significantly less likely to have a history of minipsychotic episodes than either borderline patients who did meet these criteria after exclusion of substance use or patients who did not have substance use diagnoses (see table 3).

## DISCUSSION

This study confirms clinical impressions that substance use is extremely common in borderline personality disorder. Two-thirds of our sample met criteria for at least one *DSM-III* substance use disorder, and half of the sample met criteria for two or more diagnoses. Since substance use is included in the criteria for the *DSM-III* diagnosis of borderline personality disorder, it is not surprising to find at least some substance use in patients with this disorder. It is of clinical importance, however, that over two-thirds of our subjects were substance users at the time of index admission because substance use may complicate the assessment and treatment of these patients. Our results support previous findings (1–5) from the same general time period suggesting substantial overlap between borderline personality disorder and substance use. Our data agree with the high rates of comorbid substance use reported by Andrulonis et al. (2) (69%), Pope et al. (3) (67%), and Akiskal et al. (1) (55%), although others—Frances et al. (5) (23%) and Baxter et al. (4) (11%)—have reported lower rates. Comparison with a community survey that found a 25% current prevalence rate of substance use during the early 1980s in young adults in Northeast cities (12) suggests that the rate of drug abuse in patients with borderline personality disorder is considerably higher than the rate in the general population.

The effect of using a sample of inpatients with borderline personality disorder must be considered in assessing the rate of comorbid substance use. It is possible that substance users with borderline personality

disorder may require hospitalization more frequently than nonusers with borderline personality disorder and, therefore, that substance users with borderline disorder may be overrepresented in inpatient samples. However, the patients in our sample who were not substance users had as many (if not more) previous hospitalizations than those who were substance users, which argues against this possibility. Furthermore, our results are compatible with the finding of Akiskal et al. (1) that substance use occurred in 55% of 100 outpatients with *DSM-III* borderline personality disorder.

In our sample, 96% of substance users used alcohol and/or sedative-hypnotics, suggesting that these substances may be the drugs of choice in borderline personality disorder. Without comparative data on a control group, we cannot definitively conclude that this pattern of substance preference is specific to borderline personality disorder, but two separate studies of substance use in schizophrenia conducted at our hospital (13, 14) suggested that schizophrenic patients have a distinctively different preference pattern than our subjects with borderline personality disorder. Moreover, our results are in agreement with the finding of Akiskal et al. (1) that among outpatients with *DSM-III* borderline personality disorder, 45% used sedative-hypnotics, 21% used alcohol, 19% used psychedelics (hallucinogens-cannabis-psychostimulants), and many of these outpatients used multiple drugs.

The likely influence of culture on drug of choice must be considered when interpreting our finding that patients with borderline personality disorder preferred alcohol and sedative-hypnotics. Our data on substance use in borderline personality disorder were collected on a patient sample from the early 1980s, before the more recent crack epidemic. It is possible that rates of cocaine use among borderline patients have increased over the past decade, although an unpublished retrospective study of substance abuse in borderline personality disorder also conducted at our institution found that among 76 borderline patients hospitalized between 1985 and 1988, 26 (34%) used alcohol, 17 (22%) used sedative-hypnotics, 11 (14%) used cocaine, and seven (9%) used cannabis (John Barnhill, personal communication), which suggests that current patterns of drug preference in borderline personality disorder are similar to those we report.

Several investigators (15–18) have proposed a self-medication paradigm for substance use, arguing that patients choose particular psychoactive substances because of the interaction between the psychopharmacological action of the drug and the principal painful affect associated with underlying psychopathology. This hypothesis has not been systematically studied, but Khantzian (17) has speculated that sedative-hypnotics and alcohol are used to overcome distress associated with unstable defenses against primitive narcissistic longings and aggressive impulses. Further study of drug use patterns and preferences in borderline personality disorder is necessary to elaborate the reasons borderline patients might prefer alcohol and sedative-hypnotics, but we would speculate that borderline patients use these substances because they rapidly modulate the frantic anxiety that is associated with dysphoria and anger. Interestingly, Gardner and Cowdry (19) reported a significant increase in episodes of behavioral dyscontrol in borderline patients given alprazolam compared with borderline patients given placebo. That borderline patients may prefer drugs of abuse which increase their potential for impulsive self-destructive and aggressive behavior implies that there may be differences in the immediate and longer-term effects of these substances in borderline personality disorder and suggests that borderline patients may be using these drugs for their immediate effects.

Finally, we have identified a possible subgroup of borderline patients for whom substance use is necessary to meet criteria for borderline personality disorder—whose natural course of illness may differ significantly from other borderline patients. This subgroup entered outpatient and inpatient psychiatric treatment at a more advanced age, required fewer hospitalizations, was less likely to develop transient psychotic symptoms, and met fewer diagnostic criteria for borderline personality disorder than our other subjects.

The differences between this subgroup of patients and the remainder of our sample suggest at least two hypotheses. First, this subgroup may not have borderline personality disorder. Their substance use may be primarily responsible for their psychopathology. Although these patients were diagnosed as having borderline personality disorder by treating clinicians and met chart review criteria for a diagnosis of borderline personality disorder, they were less likely than other subjects to meet criteria for some of the core symptoms of the *DSM-III* construct of the disorder. They appeared less likely to manifest an identity disturbance or suffer from chronic feelings of emptiness or boredom, better able to tolerate being alone, and engaged in fewer forms of impulsive behavior. Certainly, their unstable relationships, intense anger, affective instability, and physically self-damaging acts may be a direct consequence of substance use through state-dependent effects and/or biochemical changes in the CNS (15, 16). Substance use may be the primary cause of psychopathology for a substantial number of patients who appear to have borderline personality disorder, and others may be caught in a vicious cycle where substance use is both a cause and an effect of comorbid borderline psychopathology.

An alternative explanation for the differences in the treatment history and phenomenology of the subgroup for whom substance use is necessary to meet criteria for *DSM-III* borderline personality disorder is that they have a less severe form of borderline personality disorder than other subjects in the sample. Our data highlight the limitations of the categorical model of diagnosing borderline personality disorder (20–24), which groups persons with a range of five to eight diagnostic criteria and neglects the likely heterogeneity of members of the category. The *DSM-III* cutoff score

for the disorder was based in part on maximizing the sensitivity and specificity of the diagnosis (25). However, persons on the cutoff boundary of the diagnosis are likely to differ significantly from persons who meet most of the diagnostic criteria (26), and this may explain the differences we found between patients who did not meet *DSM-III* criteria for borderline personality disorder after exclusion of substance use and the remainder of our sample. Widiger (24) outlined a set of features (biological markers and biogenetic covariates, treatment responsivity, pervasive phenomenology, and chronic course) that could be used for research purposes to better define the borderline construct and elaborate the degree and direction of comorbidity with other psychiatric disorders.

The limitations of a retrospective method must be kept in mind when interpreting the results of this study. We are confident, however, of the diagnoses of borderline personality disorder and substance use by chart review because the chart data were reasonably complete and we were conservative in endorsing diagnostic criteria. The comparison we performed of chart review and clinical interview diagnoses for *DSM-III* substance use disorders in 13 subjects suggests that our chart review method is comparable to prospective clinical interview for identifying *DSM-III* substance use disorders in borderline personality disorder. Moreover, comprehensive prospective data on substance use in borderline personality disorder are unavailable and difficult to obtain in samples of this size.

In conclusion, our study confirms previous reports that substance use is extremely common in borderline personality disorder and suggests that borderline patients may prefer alcohol and sedative-hypnotics. We have identified differences in the treatment history and phenomenology of a large subgroup of borderline patients for whom drug use is necessary to meet criteria for borderline personality disorder. This subgroup may respond particularly well to substance use treatment. Most importantly, this study suggests a compelling need for clinicians to address the problem of substance use in their borderline patients and for the development of more effective treatment techniques for substance use in borderline personality disorder. Finally, we would emphasize the need for systematic prospective natural history and treatment studies of borderline personality disorder and comorbid substance abuse to further elaborate the relationship between substance use disorders and borderline psychopathology.

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# Childhood Sexual and Physical Abuse in Adult Patients With Borderline Personality Disorder

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*Experiences of abuse and neglect were assessed in 24 adults diagnosed as having borderline personality disorder according to the Diagnostic Interview for Borderline Patients and in 18 depressed control subjects without borderline disorder. Significantly more of the borderline patients than depressed patients reported childhood sexual abuse, abuse by more than one person, and both sexual and physical abuse. There were no between-group differences for rates of neglect or physical abuse without sexual abuse. A stepwise logistic regression revealed that derealization, diagnostic group, and chronic dysphoria were the best predictors of childhood sexual abuse in this group of patients.*

(Am J Psychiatry 1990; 147:1008–1013)

This study explores childhood abuse in adult patients with borderline personality disorder. Experiences in early childhood are viewed as important in contributing to borderline pathology (1–4). Stone (2) and Zanarini et al. (3) cited a high prevalence of childhood abuse histories in borderline patients. Herman and van der Kolk (1) noted that the symptoms of traumatically abused individuals are similar to those of patients with borderline personality disorder.

Surveys of childhood abuse reveal that the rates of a history of sexual and physical abuse may be as high as 57% in inpatients and 33% in nonclinical populations (1, 5–8). Caution is advised in interpreting these estimates, however, because methods of study and definitions of abuse differ across studies. Demographic profiles indicate that abuse occurs across economic, religious, and racial backgrounds (5, 9, 10). Although both sexes are probably at equal risk for physical abuse, risks for sexual abuse are estimated to be approximately one in three for females and one in ten for males (11, 12). Victims of physical abuse are usually preschoolers or adolescents, but sexual abuse usually begins before puberty (7, 10). Sexual abuse generally ends in mid-adolescence because the child tells someone about it, runs away, refuses to continue, or gets pregnant (13). Most abuse, both physical and sexual, is perpetrated by male relatives of the victims (7, 9).

The initial effects of sexual abuse include fear, anxiety, depression, guilt, anger, hostility, and inappropriate sexual behaviors (6, 10, 14–17). Long-term sequelae include impulsivity, self-blame, suicidal behavior, anxiety, feelings of isolation, poor self-esteem, substance abuse, sexual problems, and lack of trust in interpersonal relationships (5, 6, 8, 15). Victims of sexual abuse may direct their negative feelings against themselves, resulting in depression and self-destructive acts such as cutting, burning, and suicide attempts (12, 18).

Similar symptoms are often seen in borderline patients (*DSM-III-R*). Studies have found that female patients who had been sexually or physically victimized as children were more likely to be given a borderline diagnosis than those who had not been so victimized (16, 19). Herman et al. (20), Stone (2), and Zanarini et al. (3) found that many borderline outpatients and inpatients had a history of abuse during childhood. Westen et al. (21) found physical and/or sexual abuse documented in more than 50% of the charts of 27 inpatient adolescents with borderline personality disorder. Although sexual and physical abuse are not likely to be solely responsible for borderline pathology, they may be highly influential etiological factors.

In this study we will explore two questions related to abuse: 1) Have borderline patients experienced a greater incidence of physical, sexual, or both physical and sexual abuse during childhood than depressed patients and, if so, in what ways? 2) Are particular borderline symptoms, as measured by the Diagnostic Interview for Borderline Patients (DIB) (22), more likely to predict past occurrence of sexual abuse? We hypothesized that 1) more borderline than nonborderline patients would report sexual abuse histories, 2) sexual abuse would predict the borderline diagnosis, and 3) predictors of sexual abuse would be found among DIB

Presented in part at the 141st annual meeting of the American Psychiatric Association, Montreal, May 7–12, 1988. Received April 4, 1989; revision received Jan. 24, 1990; accepted March 1, 1990. From the Personality Disorders Program and the Biometrics Division, Department of Psychiatry, and the Department of Psychology, University of Michigan, Ann Arbor. Address reprint requests to Dr. Silk, UH-9C-9150 Box 0120, 1500 East Medical Center Drive, Ann Arbor, MI 48109-0120.

The authors thank Tom TenHave, Mark P. Becker, Ph.D., and Joel Nigg, A.C.S.W.

items relating to impulsivity, dissociative experiences, and disordered interpersonal relationships because these symptoms are reported as adult sequelae of sexual abuse (5, 6, 8, 12, 15, 18). We used depressed patients who did not have borderline personality disorder as comparison subjects because the possible overlap between depression and borderline disorder (23) renders this a more stringent test of the hypotheses.

## METHOD

Subjects were male and female inpatients between the ages of 18 and 60 at a university medical center. Patients who satisfied at least two *DSM-III* criteria for borderline personality disorder or schizotypal personality disorder or three *DSM-III* criteria for major depressive episode were considered as potential subjects. Eighty-seven percent of the eligible subjects agreed to participate. All provided informed consent. All patients were drug free, and all were given the DIB (22) by a research team member (K.R.S., N.E.L., or D.W.). Data on interrater reliability (kappa=0.80) among our group have been published elsewhere (24); reliability has been maintained through periodic retraining.

Patients who obtained a DIB score of 7 or more were included in the borderline group. This cutoff score has been shown by Frances et al. (25) to provide optimal balance between sensitivity and specificity. Subjects scoring 5 or less on the DIB were considered potential control subjects. We decided in advance to exclude subjects scoring 6 on the DIB to minimize group overlap (25).

Patients qualified for the depressed control group if, in addition to the DIB score of 5 or less, they met Research Diagnostic Criteria (RDC) (26) for probable or definite major depressive disorder on independent evaluation. RDC diagnoses were made by senior supervisors after contact with the patient and the patient's primary therapist (K.R.S. or N.E.L.). Senior supervisors were blind to the actual DIB score but were familiar with the patient's clinical presentation and history. Senior supervisors achieved an average interrater reliability on the RDC diagnosis of depression of 0.92 (weighted kappa) (27); pairwise reliability was 0.88–0.94. Exclusion criteria included organic disorders, chronic psychosis, age over 60, non-native-English-speaking, and IQ less than 70.

The patients were interviewed regarding recollections of a variety of childhood and family events by researchers blind to DIB and RDC results (S.N.O. and S.G.). The interview, the Familial Experiences Interview, was developed by one of us (S.N.O.) in collaboration with the research team. Items included physical and sexual abuse; physical neglect; loss by death, divorce, or prolonged separation; school performance difficulties; frequent moves; long periods of parental unemployment; and other events. Abuse categories included sexual abuse by mother, father, sibling, other relatives, or a nonrelated person as well as physical abuse by a caretaker and physical neglect. Sexual abuse was defined as any sexual act that included exposure to genitals with no physical contact, fondling or caressing of genitals, or penetration. Physical abuse was defined as punishment by a caretaker that produced physical marks, bruises, breaks in the skin, or an injury that warranted medical treatment regardless of whether treatment was obtained. Physical neglect included negligence by a caretaker to provide physical needs of clothing, nutrition, shelter, or proper hygiene. The interview is available on request.

Each abuse event was assessed for reported frequency, severity, duration, perceived emotional impact on the patient, age of occurrence, and type of perpetrator. Interrater reliabilities (weighted kappas) for interview items ranged from 0.47 to 1.0. The weighted kappas for all items indicating occurrence of an event ranged from 0.75 to 1.0. Weighted kappas below 0.75 were for impact, age, and severity items. Only six of 150 items had reliability of less than 0.70; none of those items was used in our analyses.

Patients cooperated with the interview and appeared invested in providing reliable information. Table 1 shows the demographic characteristics of the two groups of patients. Most of the patients in both groups were Caucasian and female. They had comparable family characteristics with regard to family size and birth order.

## RESULTS

Table 2 shows that borderline patients reported significantly higher rates of childhood sexual abuse than depressed patients. More of the borderline patients were abused by siblings, other relatives, and nonrelatives than by fathers. Physical neglect was relatively infrequent in both groups; physical abuse was relatively frequent.

All patients who reported sexual abuse described at least fondling alone or in combination with penetration. Seven (41%) of the 17 sexually abused borderline patients reported penetration; nine (53%) described being abused by different people some time during their childhood. All nine of these patients reported abuse by both a family member and a nonrelative. When physical abuse is also considered, 11 (65%) of the 17 sexually abused borderline patients described multiple abuse. In contrast, none of the four depressed patients who reported sexual abuse reported being abused by more than one person, and only three (17%) of the 18 patients recalled both sexual and physical abuse. Only women reported combined sexual abuse by a family member and physical abuse. Seven borderline patients did not report sexual abuse; four of these were men. The one man who reported sexual abuse described the abuser as a nonrelative. Nine of the 17 borderline patients who reported having experienced sexual abuse and two of the seven borderline patients

**TABLE 1. Characteristics of 24 Patients With Borderline Personality Disorder and 18 Depressed Patients Without Borderline Personality Disorder**

| Characteristic | Borderline Patients | Depressed Patients |
|---|---|---|
| Sex | | |
| Men | | |
| Number | 5 | 5 |
| Percent | 21 | 28 |
| Women | | |
| Number | 19 | 13 |
| Percent | 79 | 72 |
| Age (years)[a] | | |
| Mean | 30.0 | 42.0 |
| SD | 9.0 | 10.6 |
| Race | | |
| Caucasian | | |
| Number | 20 | 16 |
| Percent | 83 | 88 |
| Hispanic | | |
| Number | 3 | 1 |
| Percent | 13 | 6 |
| Black | | |
| Number | 1 | 0 |
| Percent | 4 | 0 |
| Native American | | |
| Number | 0 | 1 |
| Percent | 0 | 6 |
| Marital status[b] | | |
| Single | | |
| Number | 15 | 3 |
| Percent | 63 | 17 |
| Married | | |
| Number | 3 | 10 |
| Percent | 13 | 56 |
| Separated or divorced | | |
| Number | 6 | 5 |
| Percent | 25 | 28 |
| Number of siblings | | |
| Mean | 4.0 | 3.6 |
| SD | 1.7 | 1.3 |
| Birth order | | |
| Youngest | | |
| Number | 7 | 6 |
| Percent | 29 | 33 |
| Middle | | |
| Number | 9 | 6 |
| Percent | 38 | 33 |
| Oldest | | |
| Number | 8 | 6 |
| Percent | 33 | 33 |
| Hamilton Rating Scale for Depression score[c] | | |
| Mean | 14.1 | 16.6 |
| SD | 5.7 | 6.7 |
| Socioeconomic status[d] | | |
| Mean | 36.2 | 48.5 |
| SD | 13.7 | 11.5 |

[a]The difference between the two groups of patients was significant ($t=9.04$, $df=40$, $p<0.001$).
[b]The difference between the two groups of patients was significant ($x^2=11.2$, $df=2$, $p<0.01$).
[c]17-item version. Scores were available for 21 of the 24 borderline patients and 17 of the 18 depressed patients. The difference between the two groups of patients was not significant ($t=1.25$, $df=36$).
[d]Information was available for 21 of the 24 borderline patients and 13 of the 18 depressed patients. The difference between the two groups of patients was significant ($t=3.2$, $df=32$, $p<0.01$).

**TABLE 2. Type of Childhood Abuse and Perpetrator of Sexual Abuse of Borderline and Depressed Patients**

| Type of Abuse and Perpetrator[a] | Borderline Patients (N=24) | | Depressed Patients (N=18) | |
|---|---|---|---|---|
| | N | % | N | % |
| Sexual abuse[b] | 17 | 71 | 4 | 22 |
| Father | 5 | 21 | 1 | 6 |
| Mother | 1 | 4 | 0 | 0 |
| Sibling | 7 | 29 | 0 | 0 |
| Relative other than parent or sibling | 6 | 25 | 0 | 0 |
| Nonrelative | 12 | 50 | 3 | 17 |
| Physical abuse | 10 | 42 | 6 | 33 |
| Physical neglect | 4 | 17 | 1 | 6 |

[a]Percents for borderline patients add up to more than 100% because some patients suffered both sexual and physical abuse and some patients were abused by more than one person.
[b]Borderline patients had significantly higher rates of childhood sexual abuse than depressed patients ($x^2=7.88$, $df=1$, $p=0.005$).

who did not report sexual abuse met RDC criteria for major depressive disorder.

Most of the borderline patients who experienced sexual abuse reported it before age 12. The patients' mean±SD age when sexual abuse started was 7.4±2.0 years when sexual abuse was perpetrated by fathers, 8.0±2.3 when perpetrated by siblings, 9.6±3.7 when perpetrated by relatives other than parents and siblings, and 9.8±4.3 when perpetrated by nonrelatives.

A stepwise logistic regression was performed with diagnosis as the dependent variable in order to test the hypothesis that sexual abuse could predict the diagnosis of borderline personality disorder. Six variables were forced to be tested in the model until the residual variation was not significant. The predictor variables were any sexual abuse, physical abuse, physical neglect, sexual abuse perpetrated by nuclear family members (father, mother, siblings), sexual abuse perpetrated by other relatives, and sexual abuse perpetrated by nonrelatives. The regression was run first for all patients and then only for female patients because only one man reported sexual abuse. A sufficiently good fit was obtained for the model by using only sexual abuse as a predictor of diagnosis when all patients were included in the model ($\chi^2=10.18$, $df=1$, $p=0.0014$; residual variance $\chi^2=5.49$, $df=5$, $p=0.36$). Similar results were obtained for the model restricted to only women ($\chi^2=9.72$, $df=1$, $p=0.0018$; residual variance $\chi^2=7.14$, $df=5$, $p=0.21$).

To test the hypothesis that certain DIB items could predict sexual abuse, we developed a model using a stepwise logistic regression with sexual abuse as the dependent variable. Again, variables were forced to be tested in the model until the residual variation was not significant. The predictor variables were five individual DIB items: promiscuity, chronic dysphoria (as manifested by emptiness, loneliness, and boredom), derealization, depersonalization, and dependent and/or masochistic relationships, all symptoms reported in the

literature to be adult sequelae of sexual abuse (5, 6, 8, 15). Two additional predictors were devised by counting patients' positive responses to the remaining DIB items, which were divided into two categories: 1) a symptom category consisting of the remaining DIB items related to social presentation, affective functioning, and transient psychosis, and 2) a category related to more characterological symptoms, which consisted of the remaining DIB items related to impulsivity and disordered interpersonal relationships.

As before, the logistic regression was run for all patients and then only for female patients. When all patients were included, a sufficiently good fit was obtained by using only derealization and promiscuity ($\chi^2$= 25.98, df=1, p<0.0001; residual variance $\chi^2$=4.09, df=5, p=0.54). However, promiscuity by itself was not a significant predictor after derealization was in the model ($\chi^2$=0.18, df=1, n.s.). There were no patients who endorsed promiscuity who did not also endorse derealization. When only female patients were considered, a sufficient model was obtained by using only chronic dysphoria marked by emptiness, loneliness, and boredom as a significant predictor of sexual abuse ($\chi^2$=8.89, df=1, p<0.005; residual variance $\chi^2$= 11.56, df=6, p=0.07).

The stepwise logistic regression with sexual abuse as the dependent variable was repeated with the variables described but with age and diagnostic group added to the model. Age was added because there were significant between-group differences (see table 1); diagnostic group was added to avoid a tautology in our findings. When all patients were included, the results were the same as when the regression was run without including age and diagnostic group. When only female patients were included, diagnostic group (i.e., having borderline personality disorder) was the strongest significant predictor of sexual abuse ($\chi^2$=9.41, df=1, p< 0.005). Derealization by itself was also a significant predictor of sexual abuse ($\chi^2$=6.03, df=1, p<0.05), and it remained significant after diagnostic group was entered into the regression ($\chi^2$=4.94, df=1, p<0.05). A statistically significant fit ($\chi^2$=15.62, df=2, p< 0.0005) with nonsignificant residual variation ($\chi^2$= 10.95, df=7, p=0.14) was obtained with diagnostic group and derealization.

To explore the possible contributing effects of other DIB items, Yates-corrected chi-squares were calculated for all DIB items comparing patients who reported sexual abuse (N=21) with those not reporting sexual abuse (N=21). Significantly more sexually abused patients reported derealization ($\chi^2$=9.88, df=1, p= 0.002), promiscuity ($\chi^2$=4.86, df=2, p=0.028), unstable one-to-one relationships ($\chi^2$=4.76, df=1, p= 0.029), chronic dysphoria (emptiness, loneliness, or boredom) ($\chi^2$=4.43, df=1, p=0.035), and depersonalization ($\chi^2$=4.01, df=1, p=0.05). Four of the five DIB items found significant in this analysis were included in the logistic regressions, adding weight to their validity.

## DISCUSSION

Although the data on sexual abuse reported here are retrospective, we believe them to be valid. The internal consistency of the material presented by the patients and their manner of presenting it—including anxiety, tears, and affective lability—made the histories believable. Herman and Schatzow (28) reported that 74% of 53 women were able to corroborate their sexual abuse histories; another 9% found evidence suggesting that abuse had occurred in statements from other family members.

Our finding of a higher rate of reported sexual abuse in female borderline patients than in depressed patients without borderline disorder is important given the controversy surrounding the etiology of borderline personality disorder. The sexual abuse in our borderline patients, moreover, was reported to be perpetrated not only by parents. Siblings, relatives (usually cousins, grandfathers, or uncles), and nonrelatives were also perpetrators. The high prevalence of nonparental abuse could reflect chaos, lack of protection, and pathological boundaries in the families of borderline patients (29, 30). Incest with siblings may suggest collusion by patient and sibling in deviant behavior reflective of the inadequate ego and superego development of many borderline patients (31). Alternatively, reporting memories of incest by siblings, grandfathers, or uncles could be a screen for parental incest, which may be intolerable to report or recall.

Sixty-five percent of our abused borderline patients reported multiple abuses, either in the number of perpetrators of sexual abuse or in experiencing both sexual and physical abuse. The synergistic effects of different types of abuse may contribute to the severity or quality of borderline pathology. Furthermore, the fact that multiple abuse occurred supports the idea that borderline patients come from disturbed families which do not protect their members and fail to attend to the needs of their children (29).

It has been suggested that some symptoms of borderline personality disorder may reflect a history of severe and repetitive trauma (1, 2). The trauma of abuse may contribute to the borderline patient's difficulty with modulating or expressing affect. The literature suggests that individuals who have experienced extremely traumatic events fail to develop the capacity to deal effectively with emotional arousal. These people respond to such arousal with an emotional intensity disproportionate to the given situation or with severe constriction of affect (32).

The relationship between sexual abuse and dissociative phenomena, particularly derealization, was also supported by this study. Borderline patients are known to have frequent and at times severe dissociative experiences (22). Dissociative states, used defensively at the time of abuse, may become a generalized defense in any situation where strong affect is aroused. The dissociative experiences of borderline patients may relate to the severe and complete dissociation found in mul-

tiple personality disorder, a disorder empirically linked to early and severe sexual and/or physical abuse (33). However, the identity diffusion of borderline patients (31) may be confused with multiple personality disorder, and informing a suggestible borderline patient that she may have multiple personality disorder may offer a new pathological identity and lead to inappropriate treatment strategies.

These results must be considered with some reservations. Our subjects were inpatients, and it is not known if these findings can be generalized to less disturbed borderline patients, although other studies (1, 2, 20) have yielded similar findings with outpatient samples. Since all but three of our female borderline patients were sexually abused, the between-group analyses of abused and nonabused patients may not be representative. Our DIB item results, however, support findings of other research on the adult sequelae of childhood abuse (5, 6, 8, 12, 15, 18). Comorbidity of depression did not appear to affect memories of sexual abuse in our borderline patients: half of the borderline patients who reported abuse concurrently met RDC major depressive disorder criteria and half did not. Age was not a predictor of sexual abuse, even though the control subjects with major depressive disorder were significantly older. Four borderline patients who reported sexual abuse were over 40 years old; the four patients with major depressive disorder who reported sexual abuse were 40, 50, 51, and 60 years old.

Inquiry and assessment of sexual abuse experiences should become standard in evaluating borderline patients. Exploration of dissociative experiences and chronic dysphoria should be considered in relation to a history of possible sexual abuse. Inquiring about sexual abuse when patients reveal they were physically abused becomes essential.

In treatment, focusing on the relation between abuse and specific target symptoms might permit insight into particular dynamics and provide a focus for patients whose treatment can often be as disorganized as their lives. Borderline patients are highly suggestible as to the causes of their psychopathology. Therefore, the clinician must be cautious in overinterpreting abuse as the primary causal factor in patients whose biological and environmental histories are often pathogenic in multiple respects. Additionally, clinicians who pharmacologically treat borderline patients' symptoms of anxiety and depression should exercise caution in their implicit and explicit statements about etiology, since they may unintentionally collude with the family's denial of the occurrence and impact of abuse. Similarly, psychodynamic clinicians should not dismiss the patient's recollections of sexual abuse as merely oedipal wishes or fantasy.

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# Altered Platelet $\alpha_2$-Adrenergic Receptor Binding Sites in Borderline Personality Disorder

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*The authors found significantly fewer total platelet $\alpha_2$-adrenergic receptor binding sites in 13 nonmedicated patients with borderline personality disorder than in 11 patients with borderline personality disorder who were receiving low doses of benzodiazepines and 18 nonpsychiatric control subjects. The two patient groups showed comparable degrees of depression as assessed by the Hamilton Rating Scale for Depression. However, nonmedicated borderline patients were considerably more anxious than medicated patients, raising the possibility that lower $\alpha_2$-adrenergic receptor binding in borderline personality disorder is related to anxiety.*

(Am J Psychiatry 1990; 147:1014–1017)

The published studies to date on biological aspects of borderline personality disorder have primarily used neuroendocrine challenges (dexamethasone suppression and thyrotropin-releasing hormone/thyrotropin tests), EEG sleep correlates (1, 2), and measures of platelet monoamine oxidase (MAO) activity (2, 3) to explore the relationship between borderline personality disorder and major depression. However, although depressive symptoms are commonly seen in borderline personality disorder, anxiety-related symptoms are also prominent (*DSM-III*).

Putative CNS $\alpha_2$-adrenergic receptor dysfunction in both mood and anxiety disorders has led to the use of the platelet $\alpha_2$-adrenergic receptor as a marker in these disorders. The measure of $\alpha_2$-adrenergic receptor binding may be particularly relevant to biological aspects of borderline personality disorder because of the frequent occurrence of both anxiety and depressive symptoms in this disorder. In the present study, we used the selective antagonist radioligand [$^3$H]rauwolscine (4) to examine the total number of platelet $\alpha_2$-adrenergic receptor binding sites in patients with borderline personality disorder. To our knowledge, this represents the first investigation of adrenergic receptors in borderline personality disorder.

## METHOD

Twenty-four consecutively admitted patients met inclusion criteria for the study (i.e., diagnosis of borderline personality according to *DSM-III-R* and scores on the Diagnostic Interview for Borderline Patients [DIB] (5), no use of illicit substances for at least 2 weeks before the drawing of blood, and no concurrent medical illness or psychotic disorder). Thirteen of these patients were completely medication free. Eleven were being treated with acute, moderate doses of benzodiazepines at the time of blood drawing: four patients received chlordiazepoxide (25, 50, 40, and 75 mg/day, respectively), three patients received temazepam (15, 15, and 45 mg/day), one patient received 15 mg/day of diazepam, one received 0.5 mg/day of alprazolam, one received both 75 mg/day of chlordiazepoxide and 1.5 mg/day of alprazolam, and one received both 50 mg/day of chlordiazepoxide and 30 mg/day of temazepam. Diagnoses of borderline personality disorder were made by two experienced clinicians (R.Y. and S.M.M.) using *DSM-III-R* criteria and a cutoff score of 7 on the DIB (interrater agreement kappa=0.8). Severity of depressive symptoms at the time of the drawing of blood was determined by using the Hamilton Rating Scale for Depression (6). The age- and sex-comparable control group (N=18) was medication free and had no history of psychiatric illness or substance abuse as assessed by the Schedule for Affective Disorders and Schizophrenia (7).

Platelets were prepared from 50 cc of whole blood (8) and counted by a Coulter counter. The final pellet was flash frozen and stored at −70 °C. Radioligand

Presented in part at the annual meeting of the Society for Neurosciences, New Orleans, November 1987. Received Jan. 4, 1988; revisions received June 14, Sept. 27, and Dec. 13, 1989; accepted March 1, 1990. From the Post Traumatic Stress Disorder Unit, West Haven VA Medical Center, West Haven, Conn.; the Department of Psychiatry, Yale University School of Medicine, New Haven, Conn.; the Department of Psychiatry, University of Connecticut Health Center, Farmington; and the Laboratory of Developmental Neurosciences, Section of Child and Adolescent Psychiatry, The University of Chicago. Address reprint requests to Dr. Perry, Department of Psychiatry, Box 411, The University of Chicago Medical School, 5841 South Maryland Ave., Chicago, IL 60637.

Supported in part by VA research funds.

The authors thank Alex Accles and Janet Guinti for their assistance.

**TABLE 1. Platelet $\alpha_2$-Adrenergic Binding Measures in Medicated and Nonmedicated Patients With Borderline Personality Disorder and Control Subjects**

| Subjects | Site 1 | | | | Site 2 | | | | Total Receptors (sites/platelet)[c] | |
|---|---|---|---|---|---|---|---|---|---|---|
| | $K_D$ (nM) | | $B_{max}$ (sites/platelet)[a] | | $K_D$ (nM) | | $B_{max}$ (sites/platelet)[b] | | | |
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Nonmedicated patients with borderline personality disorder (N=13) | 0.34 | 0.17 | 22.0 | 11.7 | 22.4 | 4.0 | 120.3[d] | 50.1 | 142.3[d] | 56.0 |
| Medicated patients with borderline personality disorder (N=11) | 0.40 | 0.22 | 41.9[e] | 22.0 | 26.7 | 8.9 | 198.6 | 88.0 | 240.5 | 89.9 |
| Control subjects (N=18) | 0.39 | 0.17 | 26.9 | 9.6 | 25.5 | 8.6 | 192.4 | 63.7 | 219.3 | 67.4 |

[a]There was a significant difference among the three groups ($F=6.18$, $df=2, 39$, $p<0.005$).
[b]There was a significant difference among the three groups ($F=5.56$, $df=2, 39$, $p<0.007$).
[c]There was a significant difference among the three groups ($F=6.78$, $df=2, 39$, $p<0.003$).
[d]Significantly lower than control subjects and medicated borderline patients ($p<0.05$, Newman-Keuls post hoc test).
[e]Significantly greater than both the nonmedicated patients with borderline personality disorder and the control group ($p<0.05$, Newman-Keuls post hoc test).

binding assays were performed by using the antagonist radioligand [$^3$H]rauwolscine, which is approximately 20-fold more selective than yohimbine for the $\alpha_2$-adrenergic receptor (4). Frozen tissues were thawed and homogenized by sonication (Brausonic 1510) in 10-ml ice-cold 50-mM Tris buffer, pH 7.7, at 25 °C, then centrifuged (50,000 x g for 10 minutes) at 4 °C with Tris containing 50 mM of EDTA, then again with Tris and 50 mM of sodium chloride. Total binding of [$^3$H]rauwolscine (specific activity=74.05 Ci mmol, New England Nuclear) was measured in 0.3 ml aliquots of platelet membrane suspension (0.03–0.10 mg protein), which were incubated in duplicate at 25 °C for 45 minutes with 12 concentrations (0.12–35 nM) of the radioligand. Specific binding was defined as that inhibited by 100 μM(-)-norepinephrine (in 0.1% ascorbic acid) and was approximately 50%–80% in the present study. Incubation was terminated by rapid filtration over Whatman GF/B filters, which were rinsed three times with 3 ml Tris buffer. Filters were counted by liquid scintillation spectrometry with an efficiency of 33%. Raw disintegrations/minute were analyzed with a radioligand binding software package, including LIGAND (9), which determines whether the data are best fit by a single site or multisite model. Group differences in receptor measures were analyzed by analysis of variance followed by two-tailed post hoc testing using the Newman-Keuls test.

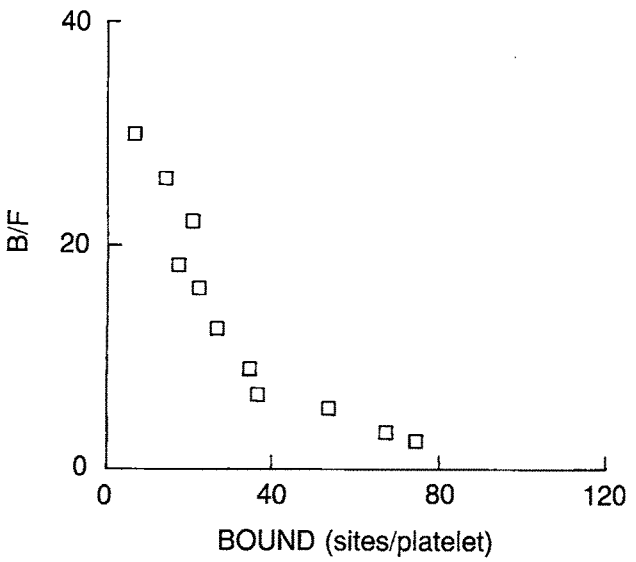
## RESULTS

There were no significant age differences between the 24 patients with borderline personality disorder (mean±SD=34.6±5.2 years, range=23–44) and the 18 normal control subjects (32.6±6.2, range=23–44).

Unconstrained LIGAND analysis of the [$^3$H]rauwolscine saturation isotherms revealed two sites of interaction: site 1 and site 2 (see table 1). A sample Scatchard transformation of the saturation isotherm is presented in figure 1. There were no group differences in the affinity ($K_D$) of [$^3$H]rauwolscine for either site 1 ($F=0.44$, $df=2, 39$, n.s.) or site 2 ($F=1.05$, $df=2, 39$, n.s.). The three groups showed significant differences in the number of total (site 1 plus site 2) $\alpha_2$-adrenergic receptor sites per platelet, owing to group differences in both site 1 and site 2 binding sites (see table 1). Specifically, nonmedicated borderline patients had significantly fewer site 2 and total binding sites than control subjects and medicated borderline patients. Furthermore, the difference in total binding sites between the medicated group and the control group was not significant (see table 1). The medicated group, however, showed a significantly greater site 1 density than both the nonmedicated patients with borderline personality disorder and the control group.

The mean Hamilton depression scale score of the nonmedicated borderline patients (23.3±10.6) could not be distinguished from that of medicated borderline patients (27.5±12.1) ($t=0.88$, $df=21$, n.s.). However, when the psychic and somatic anxiety items (items 8 and 9) of the Hamilton depression scale were summed and averaged, the nonmedicated borderline patients reported a 58% higher anxiety score than did the medicated borderline patients (2.69±0.52 versus 1.7±0.52, respectively) ($t=1.32$, $df=21$, n.s.). Regression analysis of all patients with borderline personality disorder failed to reveal any significant correlation between the number of sites and the anxiety measure. However, when the nonmedicated and medicated groups were considered separately, there was a significant correlation between the site 2 density and Hamilton depression scale anxiety items 8 and 9 in the nonmedicated borderline patients ($r=0.56$, $df=12$, $p<0.05$). In contrast, there were no significant correlations between depression as assessed by total Hamilton depression scale scores and number of binding sites in the patient groups.

**FIGURE 1. Representative Scatchard Transformation of [$^3$H] Rauwolscine Specific Binding to Platelet $\alpha_2$-Adrenergic Receptor Sites[a]**




[a]B/F=bound/free.

## DISCUSSION

To our knowledge, the present findings represent the first report of $\alpha_2$-adrenergic receptor binding in borderline personality disorder. Nonmedicated borderline patients had significantly fewer [$^3$H]rauwolscine binding sites than normal control subjects. In contrast, the total number of [$^3$H]rauwolscine binding sites in benzodiazepine-treated borderline patients was comparable to the number observed in normal control subjects.

Like many receptor systems, the $\alpha_2$-adrenergic receptor/effector complex consists of both a receptor/recognition site, or free receptor site, and a nucleotide-binding protein heterotrimer. The binding of the free receptor site to this protein heterotrimer affects a third component of the receptor system, the catalytic moiety of adenylate cyclase (10, 11). Previous studies have demonstrated that the [$^3$H]rauwolscine site 1 corresponds to the free receptor recognition site, or $\alpha_2$-(L), and the [$^3$H]rauwolscine site 2 corresponds to the receptor site nucleotide-binding protein complex, or $\alpha_2$-(H) (12).

The lower density of total receptor sites in the nonmedicated borderline patients, primarily due to fewer of the $\alpha_2$-(H) sites, may reflect a chronic overexposure to catecholamines in these patients. Chronic exposure to high levels of catecholamine results in loss of membrane receptor in many in vitro cell systems and also in vivo in the brain (13, 14). Furthermore, a lower density of $\alpha_2$-adrenergic receptor binding sites has been reported in several chronic stress disorders, such as congestive heart failure (15), posttraumatic stress disorder (16), and panic-anxiety (17), which are characterized by hypercatecholaminergic states. Clinically, borderline patients often appear to be chronically stressed; thus, they may share certain biological similarities with other patients with chronic stress disorders. In this regard, one recent study (18) suggested that borderline personality disorder in some patients may be associated with early childhood trauma.

Interestingly, the benzodiazepine-treated borderline patients were less anxious than the nonmedicated patients as measured by the Hamilton depression scale and did not have fewer total receptors than normal control subjects. The direct effects of benzodiazepine at the $\alpha_2$-receptor are minimal (12), and it is likely that the effects in this study were indirect. Benzodiazepines interact with central noradrenergic systems, decreasing sympathetic activity (19). Thus, in the present study of "anxious" patients, benzodiazepine treatment may have decreased overall peripheral sympathetic activity.

Comparison of the present results with those reported elsewhere for major depressive disorder is difficult; however, no laboratories have reported down-regulated platelet $\alpha_2$-receptors to this extent in major depressive disorder. In the present study, nonmedicated and medicated patients with borderline personality disorder had similar Hamilton depression scores. Thus, the observed group differences in $\alpha_2$-receptor binding site number were not linked to "depressive" pathophysiology. Rather, our findings may be more reflective of the greater anxiety (and greater sympathetic arousal) in the nonmedicated patients with borderline personality disorder.

The present results are preliminary, but they suggest that further studies addressing the specificity of adrenergic receptor functioning in borderline personality disorder, major depressive disorder, and other affective disorders are needed.

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# Diagnosis of Major Depression in Cancer Patients According to Four Sets of Criteria

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*Diagnoses of major depression in 152 cancer patients differed as much as 13% depending on the diagnostic system used. The Beck Depression Inventory and the Hamilton Rating Scale for Depression were useful tools for screening patients with depressive symptoms but frequently misclassified those who had no major depression according to one or more of the criteria-based diagnostic systems.*

(Am J Psychiatry 1990; 147:1021–1024)

Several sets of diagnostic criteria have been used to identify patients with major depression. Perhaps the most commonly used are the *DSM-III* and *DSM-III-R* criteria and the Research Diagnostic Criteria (RDC) (1). The subpopulation of patients diagnosed as having major depression differs, however, depending on which diagnostic system is used (2). This problem of consistency in diagnosis is compounded in patients who have depression associated with medical illness. Depression has been identified in 2%–45% of these patients, depending on the method used to make the diagnosis (3). Such variability in diagnosis leads to uncertainty in the clinical setting about who should receive treatment and who should not. The purpose of this study was to investigate the relation of scores on commonly used self- and observer-rated depression scales (the Beck Depression Inventory [4] and the Hamilton Rating Scale for Depression [5]) to the presence or absence of criteria-based diagnoses of depression in medically ill patients.

## METHOD

In an investigation of the treatment of depression in patients with terminal solid tumors, 152 (19%) of 808 patients reported symptoms of depression during clinical evaluation or screening with the Hamilton scale (N=83) and/or the Beck inventory (N=77). The mean± SD age of these patients was 59±14 years, with a range of 16–88 years. Eighty-nine (59%) of the patients were women, and all of the patients had potentially fatal solid tumors at various stages.

The 152 patients were given a structured screening questionnaire for depression according to the *DSM-III* and *DSM-III-R* criteria and the RDC. All three of these sets of criteria exclude the diagnosis of major depression if an organic factor may be involved. This exclusionary criterion was not used in this sample, since all of the subjects had cancer. The presence of organic mood disorder was not assessed because the criteria were considered too loosely defined. For purposes of this study, symptoms were recorded, if present, regardless of etiology (related or unrelated to medical condition) for *DSM-III* and RDC diagnoses. If a definite relationship between a symptom and the physical condition was present, then that symptom was not used in diagnosing depression according to *DSM-III-R*. We were also able to identify depression retrospectively according to the Endicott criteria (6), although the substitution symptom "reactive mood" was often not well documented.

Differences in parametric scores were assessed by t tests, and nonparametric scores were assessed by chi-square tests. Correlations of depression scale scores were made using a correlation coefficient. Differences were considered significant when the 95% confidence level was reached.

## RESULTS

Roughly one-third of the 152 patients screened for symptoms of depression met the criteria for major depression according to one or more of the four diagnostic systems (tables 1 and 2).

Patients with major depression (N=38–58) were significantly younger (54 versus 61 years) than those with depressive symptoms only (N=94–114), regardless of the diagnostic system (e.g., the mean±SD age for the patients with major depression according to *DSM-III* was 55.3±14.9 years and for the patients without that *DSM-III* diagnosis, 61.9±12.1 years; t=2.97, df=149,

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Supported in part by a grant from the Upjohn Company.

The authors thank Peter Debelius-Enemark and Deborah Pfab for assistance in data collection and management.

**TABLE 1. Depression Scores of 152 Cancer Patients With Depressive Symptoms Who Were or Were Not Given Diagnoses of Major Depression According to *DSM-III* and *DSM-III-R***

| | *DSM-III* | | | | | | | *DSM-III-R* | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Diagnosis (N=58) | | No Diagnosis (N=94) | | Analysis | | | Diagnosis (N=45) | | No Diagnosis (N=106) | | Analysis | | |
| Measure | Mean | SD | Mean | SD | t | df | p | Mean | SD | Mean | SD | t | df | p |
| Beck inventory (N=77)[a] | | | | | | | | | | | | | | |
| Total | 22.1 | 9.3 | 11.9 | 7.5 | 5.11 | 75 | <0.0001 | 22.6 | 9.6 | 13.7 | 8.3 | 4.33 | 74 | <0.0001 |
| Items 1–14 | 11.8 | 6.7 | 4.3 | 4.5 | 5.96 | 75 | <0.0001 | 12.5 | 6.9 | 5.4 | 5.0 | 5.12 | 74 | <0.0001 |
| Items 15–21 | 10.3 | 4.2 | 7.7 | 3.9 | 2.73 | 75 | 0.008 | 10.1 | 4.3 | 8.4 | 4.1 | 1.90 | 74 | 0.06 |
| Hamilton scale total (N=83)[a] | 24.0 | 6.3 | 11.5 | 6.0 | 8.89 | 81 | <0.0001 | 24.0 | 6.7 | 14.3 | 7.6 | 6.29 | 80 | <0.0001 |

[a]Eight patients were assessed with both the Beck Depression Inventory and the Hamilton Rating Scale for Depression.

**TABLE 2. Depression Scores of 152 Cancer Patients With Depressive Symptoms Who Were or Were Not Given Diagnoses of Major Depression According to the Research Diagnostic Criteria and the Endicott Criteria**

| | Research Diagnostic Criteria | | | | | | | Endicott Criteria | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Diagnosis (N=38) | | No Diagnosis (N=114) | | Analysis | | | Diagnosis (N=55) | | No Diagnosis (N=97) | | Analysis | | |
| Measure | Mean | SD | Mean | SD | t | df | p | Mean | SD | Mean | SD | t | df | p |
| Beck inventory (N=77)[a] | | | | | | | | | | | | | | |
| Total | 24.2 | 10.1 | 14.0 | 7.6 | 5.01 | 75 | <0.0001 | 22.1 | 9.5 | 12.6 | 7.8 | 4.74 | 75 | <0.0001 |
| Items 1–14 | 13.7 | 7.2 | 5.7 | 4.8 | 5.31 | 75 | <0.0001 | 11.9 | 6.8 | 4.7 | 4.8 | 5.45 | 76 | <0.0001 |
| Items 15–21 | 10.6 | 4.4 | 8.4 | 4.0 | 2.29 | 75 | 0.02 | 10.2 | 4.3 | 7.9 | 3.9 | 2.49 | 75 | 0.02 |
| Hamilton scale total (N=83)[a] | 24.9 | 6.8 | 15.5 | 7.6 | 5.69 | 81 | <0.0001 | 23.7 | 6.3 | 12.4 | 7.0 | 2.70 | 81 | <0.0001 |

[a]Eight patients were assessed with both the Beck Depression Inventory and the Hamilton Rating Scale for Depression.

p=0.003). Women who had symptoms of depression on screening were no more likely to have major depression (e.g., 34 of 89 had a *DSM-III* diagnosis) than men (e.g., 24 of 63 had a *DSM-III* diagnosis), except when diagnoses were made according to the RDC (28 of 89 versus 10 of 63; $\chi^2=3.98$, df=1, $p<0.05$, with Yates' correction).

A Beck inventory total score of less than 11 predicted with 93% certainty that patients would not have a diagnosis of major depression according to *DSM-III*, the RDC, and the Endicott criteria but not *DSM-III-R* (table 3). If the prevalence of major depression, however, is estimated to be 15% in patients with medical illness, then the negative predictive value for a Beck inventory score of less than 11 is over 99%. High total scores on the Beck inventory (>25) and the Hamilton scale (>19) were associated with higher proportions of patients receiving diagnoses of major depression; however, the percentage who met criteria varied considerably depending on the diagnostic system used. The percentage with major depression dropped substantially when Beck inventory and Hamilton scale scores fell between 11 and 25 and between 15 and 19, respectively (table 3). The percentage correctly identified as having major depression even with high scores (positive predictive value) is substantially reduced if prevalence is estimated to be 15%.

The sum of scores on the first 14 items of the Beck inventory (psychological items) was no better at identifying patients with major depression than was the total Beck score (table 3). The correlation (r) between the two was 0.93 (df=78, $R^2=0.87$, $p<0.00001$). The sum of scores on items 15–21 (somatic factors) also differentiated patients with major depression from those with depressive symptoms only but was much less discriminating (table 3). The correlation (r) between scores on items 1–14 and items 15–21 was only 0.55 (df=78, $R^2=0.30$, $p<0.00001$). High Hamilton scale scores were comparable to Beck inventory scores in identifying those who would meet the *DSM-III* criteria for depression (positive predictive values of 95% and 94%, respectively, when uncorrected for prevalence). However, since 42 patients had scores greater than 19 on the Hamilton scale, while only 17 had scores greater than 25 on the Beck inventory, the Hamilton scale allowed a greater number to be assessed with the positive predictive value.

## DISCUSSION

This study was a preliminary investigation into differences in the frequency of the diagnosis of major depression in patients with medical illness (cancer) depending on the diagnostic criteria used and their relationship to screening questionnaires. Endicott (6) sug-

**TABLE 3. Relation of 152 Cancer Patients' Depressive Symptoms to Diagnoses of Major Depression According to Four Sets of Criteria**

| | Patients With Major Depression | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | According to *DSM-III* (N=58, or 38%) | | According to *DSM-III-R* (N=45, or 30%) | | According to Research Diagnostic Criteria (N=38, or 25%) | | According to Endicott Criteria (N=55, or 36%) | |
| Depression Scale Score | N | % | N | % | N | % | N | % |
| Beck inventory (N=77)[a] | | | | | | | | |
| Total | | | | | | | | |
| <11 (N=14) | 1 | 7 | 0 | 0 | 1 | 7 | 1 | 7 |
| 11–25 (N=46) | 28 | 61 | 22 | 49[b] | 15 | 33 | 27 | 59 |
| >25 (N=17) | 16 | 94 | 13 | 76 | 13 | 76 | 15 | 94[b] |
| Items 1–14 | | | | | | | | |
| <4 (N=19) | 1 | 5 | 1 | 5 | 0 | 0 | 1 | 5 |
| 4–13 (N=39) | 27 | 69 | 20 | 53[b] | 15 | 38 | 26 | 67 |
| >13 (N=19) | 17 | 89 | 15 | 79 | 15 | 79 | 16 | 89[b] |
| Items 15–21 | | | | | | | | |
| <6 (N=15) | 3 | 20 | 2 | 13 | 2 | 13 | 3 | 20 |
| 6–11 (N=39) | 25 | 64 | 21 | 55[b] | 16 | 41 | 24 | 62 |
| >11 (N=23) | 17 | 74 | 13 | 57 | 11 | 48 | 16 | 73[b] |
| Hamilton scale total (N=83)[a] | | | | | | | | |
| <15 (N=24) | 2 | 8 | 2 | 8 | 2 | 8 | 2 | 8 |
| 15–19 (N=17) | 11 | 65 | 10 | 59 | 6 | 35 | 12 | 71 |
| >19 (N=42) | 40 | 95 | 31 | 76[b] | 26 | 62 | 38 | 93[b] |

[a]Eight patients were assessed with both the Beck Depression Inventory and the Hamilton Rating Scale for Depression.
[b]Percent based on N=1 less than the N given in the left-hand column.

gested that substituting psychological symptoms for somatic ones when the latter might be due to physical illness might improve the ability to identify patients with "true depression." Our assessment of patients included only three of the four substitute criteria proposed by this author. Even so, there was a great deal of overlap of patients given the diagnosis according to the Endicott and the *DSM-III* criteria. Consistent reporting of patients who met the additional criterion, reactive mood, could have increased the number of patients classified as having major depression according to the Endicott criteria.

*DSM-III-R* criteria exclude symptoms if they are definitely related to a physical condition. This exclusionary rule decreased the percentage of patients identified as having major depression to 30% from the 38% identified according to *DSM-III*; however, no validation of this distinction has been made. Our findings with respect to the somatic items from the Beck inventory suggest that exclusion of somatic symptoms may improve the ability to identify patients with major depression by deleting "noise" from the data collected. This is especially true because somatic items make up a considerable portion (four of nine) of the criteria for major depression in *DSM-III-R*. However, if somatic symptoms are deleted but the number of symptoms required for diagnosis is not decreased, the diagnosis becomes much more rigorous. Whether this is appropriate or whether substitutions should be made, as suggested by Endicott, is a question for future research to answer.

The most stringent RDC identified fewer patients with major depression than did the other classification systems. Twenty (13%) of the 152 cancer patients who had major depression according to *DSM-III* (17 according to the Endicott criteria) did not have it according to the RDC. This substantial difference points to the fact that the RDC identify patients with more severe depression.

Our findings do not suggest that one classification system is better than another but point out that classification systems identify overlapping populations which can vary significantly in size and consistency. At this time there is no evidence that one is more valid than another in a medically ill population such as the one we studied. The next obvious step is to include validating parameters (demographic variables, personal and family history, course of illness, and response to treatment) along with discriminant diagnoses to determine whether one diagnostic system is clinically superior.

As expected, the Beck inventory and the Hamilton scale both yielded higher scores for patients with major depression regardless of the classification system. Neither, however, could discriminate patients with major depression from patients with depressive symptoms only until relatively high scores were achieved. Even then, discrimination was limited unless the *DSM-III* and Endicott criteria were used. This was true even when the Beck inventory scores were separated into psychological (items 1–14) and somatic (items 15–21) categories. Our data therefore suggest that symptom scales are better for *screening* those at risk for depression than they are for identifying its presence or ab-

sence. The possibility of accurate diagnosis of depression in the medically ill by using symptom checklists or scale scores, as has frequently been done in the past (3), is not supported by our data. A good clinical history remains an essential part of the psychiatric evaluation of patients with medical illness in whom depression is a diagnostic consideration.

There has always been concern about how much somatic symptoms contribute to the diagnosis of depression in patients whose depression is associated with medical illness. Our results suggest that the relationship of psychological symptoms to somatic symptoms, as in the Beck inventory, in patients with cancer is quite close. Inclusion of somatic symptoms in a symptom assessment, as occurs not only in the Beck inventory and the Hamilton scale but also in criteria-based diagnostic systems, therefore does not detract from the ability to differentiate depressed from nondepressed patients. For purposes of efficiency, inclusion of only psychological symptoms as long as they are sufficiently severe and persistent, as suggested by Endicott, is probably the best approach for these patients; however, this is not yet widely done in the current practice of psychiatry.

In summary, this preliminary investigation of depression associated with terminal solid tumors showed that the Endicott criteria (6), designed to diagnose major depression in the medically ill by substituting psychological symptoms for the somatic ones in *DSM-III*, identified a population similar to that identified by the *DSM-III* criteria; however, major depression was diagnosed much less frequently when *DSM-III-R* and the RDC were used. The relation of scores on the Beck Depression Inventory and the Hamilton Rating Scale for Depression to the presence of these criteria-based diagnoses suggested that these self- and observer-rated scales could be used to screen patients at risk for major depression associated with medical illness but not to make the diagnosis.

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# Syndrome Comorbidity in Patients With Major Depression or Dysthymia: Prevalence and Temporal Relationships

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*The authors administered the Structured Clinical Interview for DSM-III-R to 260 patients with principal diagnoses of depressive disorders. Approximately two-thirds of these patients were given at least one additional concurrent axis I disorder. The most common comorbid diagnoses were anxiety disorders. The depressive disorders preceded the anxiety disorders in most patients. The authors not only point out the scientific and clinical implications of psychiatric comorbidity in view of the patterns of comorbidity found in this and previous studies but also discuss issues in comorbidity research.*

(Am J Psychiatry 1990; 147:1025–1028)

There is considerable evidence that patients with principal diagnoses of depressive disorders (i.e., major depression or dysthymia) manifest a variety of nondepressive symptoms as well (1–4). The most frequent nondepressive symptoms reported by patients with depressive disorders are those typically associated with anxiety (2–4). However, due to the hierarchical exclusionary rules in former classification systems such as the 1980 version of *DSM-III*, coexisting (comorbid) nondepressive symptoms were usually ignored as signs of a separate disorder because they were believed to be related to the depressive disorder that occupied a higher position in the hierarchy. For example, the presence of panic attacks did not require the diagnosis of panic disorder if the clinician judged that the panic attacks were due to major depression. In fact, according to *DSM-III*, the presence of major depression could exclude any of the anxiety disorders as well as many other disorders that occupied a lower status on the hierarchy.

Until the appearance of *DSM-III-R*, syndrome comorbidity—the presence of concurrent independent psychiatric disorders—was largely ignored. However, most of the hierarchical exclusionary rules used in *DSM-III* were dropped in *DSM-III-R*, allowing clinicians to give "multiple diagnoses when different syndromes occur together in one episode of illness" (*DSM-III-R*, p. xxiv). In cases of comorbidity, principal status is determined on the basis of relative severity and interference with functioning.

Patterns of comorbidity have important clinical implications. The course and response to treatments of a patient with more than one diagnosis may differ from that of a patient with only one diagnosis. For example, in a recent review, Grunhaus (5) concluded that patients with diagnoses of both panic disorder and major depression have more severe symptoms than, exhibit a greater degree of psychopathology over time than, and do not respond as well to conventional antidepressants as do patients with major depression alone.

In addition to practical clinical implications, patterns of comorbidity have important scientific implications as well. The co-occurrence of certain disorders may provide information about the etiology of the disorders. For example, the frequent co-occurrence of obsessive-compulsive disorder and depressive disorders might indicate that a common vulnerability underlies both disorders. The etiology of illness in these patients may be quite different than it is in patients with either disorder alone or in patients with comorbid depressive and panic disorders. Patterns of comorbidity also affect genetic epidemiology. Relatives of individuals with a pattern of comorbid major depression and anxiety disorder are at greater risk for developing one of these disorders than are relatives of individuals with major depression without anxiety disorder (6).

Studies investigating the prevalence and patterns of syndrome comorbidity among patients with principal diagnoses of anxiety disorders have consistently demonstrated that approximately two-thirds of these patients have at least one additional axis I disorder and that there are consistent patterns of co-occurrence (7–9). In view of the high rates of syndrome comorbidity found in these studies, it appears that the practice of assigning multiple diagnoses is in most cases essential to convey the overall level of psychopathology present in patients with anxiety disorders.

Less research has been done investigating syndrome comorbidity among depressive disorders, especially dysthymia, using *DSM-III-R* criteria. For example, although Leckman et al. (10), using the research diag-

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nostic criteria of Feighner et al. (11), found that 58% of patients with diagnoses of major depression were also given the diagnoses of generalized anxiety disorder, panic disorder, or agoraphobia, it is not known whether findings from studies using these criteria can be applied to the current classification system. In a more recent study using *DSM-III* criteria (but suspending the hierarchical rules, as recommended by *DSM-III-R*), DiNardo and Barlow (12) found that eight of 11 patients with principal diagnoses of major depression and seven of nine patients with dysthymia had at least one additional disorder. However, the focus of this study was on anxiety disorders; therefore, the sample size of the depressed patients was too small to draw any firm conclusions. More importantly, since the depressed patients in this study were being treated in an anxiety disorders clinic, the prevalence of coexisting anxiety disorders may have been higher than it would be in most depressed patients. The results observed, therefore, may not generalize to the majority of depressed patients.

The present descriptive study has two major aims: 1) to examine the prevalence and pattern of syndrome comorbidity in a large number of patients given principal diagnoses of major depression or dysthymia according to *DSM-III-R* criteria (N=260) and 2) to examine the temporal relationship of disorders that occur together in these patients.

## METHOD

All of the patients evaluated at the Center for Cognitive Therapy, an outpatient clinic at the University of Pennsylvania School of Medicine, who received principal diagnoses of major depression or dysthymia during 1988 and the first half of 1989 were included in this study. Patients were either self-referred to the clinic or referred by a physician. A total of 576 patients were evaluated with the Structured Clinical Interview for DSM-III-R (SCID) (13) by a psychologist during the study time period. Of these, 197 were given principal diagnoses of major depression (111 women and 86 men; mean±SD age=36.4±12.0 years), and 63 were given principal diagnoses of dysthymia (33 women and 30 men; mean age=38.4±9.9 years). Informed consent was obtained from all patients.

All diagnoses were made in strict accordance with *DSM-III-R* criteria. In order to confirm the axis I diagnosis or diagnoses, all interviewers consulted with a senior staff psychologist who conducted a brief clinical interview with the patient.

When two or more disorders were judged to be present (comorbidity), the *principal* diagnosis was determined on the basis of relative severity and interference with functioning, as recommended in *DSM-III-R*. In cases of comorbidity, intake evaluators also rated the relative onset of the diagnosed disorders on the basis of the patient's historical report during the assessment. The *primary* disorder was that which occurred chronologically before all other disorders.

**TABLE 1. Comorbid Diagnoses Among 260 Patients With Depressive Disorders**

| | Principal Diagnosis | | | |
|---|---|---|---|---|
| | Dysthymia (N=63) | | Major Depression (N=197) | |
| Comorbid Diagnosis | N | % | N | % |
| Anxiety disorder | 30 | 47.6 | 82 | 41.6 |
| Panic disorder with agoraphobia | 2 | 3.2 | 13 | 7.0 |
| Panic disorder without agoraphobia | 2 | 3.2 | 6 | 3.0 |
| Agoraphobia without panic disorder | 0 | 0.0 | 4 | 2.0 |
| Social phobia | 17 | 27.0 | 30 | 15.2 |
| Simple phobia | 2 | 3.2 | 4 | 2.0 |
| Obsessive-compulsive disorder | 0 | 0.0 | 8 | 4.1 |
| Posttraumatic stress disorder | 0 | 0.0 | 0 | 0.0 |
| Generalized anxiety disorder | 14 | 22.2 | 40 | 20.3 |
| Substance abuse/dependence | 7 | 11.1 | 30 | 15.2 |
| Alcohol | 7 | 11.1 | 16 | 8.1 |
| Cocaine | 0 | 0.0 | 4 | 2.0 |
| Amphetamine | 0 | 0.0 | 2 | 1.0 |
| Cannabis | 0 | 0.0 | 2 | 1.0 |
| Polysubstance | 0 | 0.0 | 6 | 3.0 |
| Adjustment disorder | 1 | 1.6 | 2 | 1.0 |
| Somatoform disorder | 1 | 1.6 | 1 | 0.5 |
| Sleep disorder | 0 | 0.0 | 1 | 0.5 |
| Sexual disorder | 2 | 3.2 | 0 | 0.0 |
| Dissociative disorder | 0 | 0.0 | 0 | 0.0 |

## RESULTS

Forty-one (65%) of the 63 patients with principal diagnoses of dysthymia and 116 (59%) of the 197 patients with principal diagnoses of major depression were given at least one additional axis I diagnosis. The most common comorbid axis I diagnoses were anxiety disorders (see table 1). Among the anxiety disorders, social phobia and generalized anxiety disorder were the most frequently assigned additional diagnoses.

Just over 10% of the patients with dysthymia received additional diagnoses of substance abuse or dependence—all related to alcohol. However, nearly half of the patients with major depression who received additional diagnoses of substance abuse or dependence used substances other than or in addition to alcohol.

Additional diagnoses from the remaining diagnostic categories (i.e., adjustment, somatoform, sleep, sexual, and dissociative disorders) were rarely assigned.

The onset of the depressive disorder preceded the onset of the anxiety disorder in 23 (77%) of the 30 patients with dysthymia and an anxiety disorder and 49 (60%) of the 82 patients with major depression and an anxiety disorder. The anxiety disorder preceded the

**TABLE 2. Comorbid Diagnoses of Patients With Depressive Disorders Whose Primary Comorbid Diagnosis Preceded the Principal Depressive Disorder Diagnosis**

| | Principal Diagnosis | | | | | |
|---|---|---|---|---|---|---|
| | Dysthymia | | | Major Depression | | |
| | | Comorbid Diagnosis Is Primary | | | Comorbid Diagnosis Is Primary | |
| Comorbid Diagnosis | N | N | % | N | N | % |
| Anxiety disorder | | | | | | |
| Panic disorder with agoraphobia | 2 | 0 | 0 | 13 | 1 | 8 |
| Panic disorder without agoraphobia | 2 | 0 | 0 | 6 | 1 | 17 |
| Agoraphobia without panic disorder | —[a] | — | — | 4 | 1 | 25 |
| Social phobia | 17 | 3 | 18 | 30 | 11 | 37 |
| Simple phobia | 2 | 0 | 0 | 4 | 1 | 25 |
| Obsessive-compulsive disorder | —[a] | — | — | 8 | 0 | 0 |
| Generalized anxiety disorder | 14 | 4 | 29 | 40 | 18 | 45 |
| Substance abuse/dependence | 7 | 0 | 0 | 30 | 10 | 33 |
| Adjustment disorder | 1 | 0 | 0 | 2 | 0 | 0 |
| Somatoform disorder | 1 | 0 | 0 | 1 | 0 | 0 |
| Sexual disorder | 2 | 0 | 0 | —[a] | — | — |

[a]This disorder was not diagnosed as an additional disorder in patients with this principal diagnosis.

depressive disorder in only seven (23%) of the patients with dysthymia and an anxiety disorder and 33 (40%) of the patients with major depression and an anxiety disorder.

Table 2 presents the comorbid diagnoses of patients with depressive disorders whose comorbid diagnosis chronologically preceded the depressive disorder. The most frequent disorder to precede the depressive disorder was generalized anxiety disorder.

## DISCUSSION

The results of this study indicate that most patients with principal diagnoses of depressive disorders have a variety of nondepressive disorders as well. Anxiety disorders are the most frequently assigned additional diagnoses, followed by substance abuse disorders. In the majority of patients with comorbid disorders, the depressive disorder preceded the onset of the additional diagnoses.

The pattern of comorbidity observed in the present study is similar to that found by DiNardo and Barlow (12), who used *DSM-III* criteria and, to our knowledge, were the only other group to include patients with dysthymia and major depression. Overall, for patients with depressive disorders, generalized anxiety disorder was the most commonly assigned additional diagnosis, followed by social phobia and panic disorder (with and without agoraphobia). For patients with dysthymia, social phobia was the most frequently assigned additional diagnosis in both studies. Generalized anxiety disorder was the most frequently assigned additional diagnosis for patients with major depression in both studies. However, the overall rate of additional anxiety disorder diagnoses was much higher in the DiNardo and Barlow study (12) than in ours. For example, although generalized anxiety disorder was the most frequently assigned additional diagnosis for patients with major depression in both studies, 45% of patients in the DiNardo and Barlow study were diagnosed with this comorbid pattern, compared with 20% in our present study. This is probably due to the fact that depressed patients in the DiNardo and Barlow study were treated in an anxiety disorders specialty clinic, suggesting that anxiety symptoms may have been more prominent in these patients than in most depressed patients.

In view of these findings of a high rate of syndrome comorbidity among patients with depressive disorders, in addition to the findings of several other studies indicating high rates of syndrome comorbidity among patients with anxiety disorders (7–9, 12), it appears that the practice of assigning one diagnosis is inadequate to convey the typical patient's overall level of psychopathology. As noted by Maser and Cloninger (14), "Prototypic descriptions of patients with specific disorders are often extreme oversimplifications of the multifaceted clinical profile of patients who receive that diagnosis." Therefore, the revision in *DSM-III-R* of the hierarchical exclusionary system, allowing for multiple diagnoses, appears to be necessary to accurately describe the overall clinical picture.

An examination of the temporal relationship of the principal depressive disorder and the additional diagnoses revealed that for most patients the onset of the depressive disorder chronologically preceded the onset of the additional diagnoses. This was true for 77% of the patients with comorbid dysthymia and anxiety disorders and for 60% of the patients with comorbid major depression and anxiety disorders. Therefore, the results of the present study indicate that a large number of patients with a chronologically primary depressive disorder do in fact go on to develop additional psychiatric disorders. This is contrary to the data of Cloninger et al. (15), who found that patients with a chronologically primary depressive disorder rarely develop secondary (or additional) diagnoses. One possible reason for the discrepant results is that Cloninger et al. used criteria similar to Research Diagnostic Criteria (16), whereas *DSM-III-R* criteria were used in the present study. Another possibility is that our present study relied on the patient's retrospective recall to determine the relative onset of the disorders, whereas Cloninger et al. interviewed patients on separate occasions. Data concerning the temporal relationship of comorbid disorders in the present study must be interpreted with caution because they are based on retrospective recall, which is subject to distortion. For example, previous research has shown that a depressed

mood state influences the recall of information (17) and thus may interfere with the ability of a patient to convey the true temporal relationship. On the other hand, there is evidence that it is possible to obtain reliable lifetime diagnoses in a nonpatient population (18) as well as in patients with anxiety disorders, including those who have a comorbid diagnosis of major depression (19). Clearly, longitudinal research using the present classification system is necessary to determine the true temporal relationships of principal and additional psychiatric disorders.

The patterns of temporal onset found in the present study are consistent with what would be expected on the basis of research concerning the age at onset of these disorders. The finding that among anxiety disorders, generalized anxiety disorder and social phobia are the most likely to precede the onset of the principal depressive disorder is to be expected on the basis of previous research demonstrating the earlier onset of these two disorders compared with other anxiety disorders (20). The finding observed in the present study that dysthymia was more likely than major depression to precede comorbid anxiety disorders is consistent with the notion that dysthymia often begins in late childhood or adolescence (*DSM-III-R*) and thus is presumably more likely to predate any other additional disorders, which often have a later onset.

In the light of the important scientific and clinical implications of psychiatric comorbidity noted here, there has been a recent increase in interest in this area (14). Presumably, during the next few years there will be an increase in research studies examining this topic. In order to avoid confusion in future research, we suggest that an important distinction consistently be made between the terms "principal diagnosis" and "primary diagnosis." *DSM-III-R* specifies that "the *principal* diagnosis is the condition that was chiefly responsible for occasioning the evaluation . . . . In most cases this condition will be the main focus of attention or treatment" (*DSM-III-R*, p. 17). Therefore, the principal diagnosis should be reserved to indicate the most severe disorder at the present time. We think that the term "primary diagnosis" should be reserved for the diagnosis that chronologically preceded all other diagnoses. To date, the term "primary diagnosis" is often used to indicate different concepts. For example, some investigators have used it to indicate relative severity of comorbid disorders (7, 8, 10), but other investigators use the term to indicate temporal primacy of comorbid disorders (15).

Relative severity and temporal sequence of psychiatric disorders have important clinical and theoretical implications; therefore, both should be specified in all patients. For example, the genetic epidemiology, course, and treatment of a patient with comorbid major depression and panic disorder may be different depending on the chronological onset of the disorders (i.e., whether major depression developed secondary to panic disorder or panic disorder developed secondary to major depression) (14). Reserving the terms "principal diagnosis" (in contrast to additional diagnosis) to indicate relative severity and "primary diagnosis" (in contrast to secondary, tertiary, etc.) to indicate temporal sequence of psychiatric disorders will allow these important distinctions to be made without confusion and thus will facilitate progress in our understanding of this area.

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# Evidence for Less Improvement in Depression in Patients Taking Benzodiazepines During Unilateral ECT

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*Among 48 patients with diagnoses of depression according to* DSM-III, *there was a significant relation between therapeutic failure of unilateral ECT, as measured by scores on the Hamilton Rating Scale for Depression, and the concomitant use of a benzodiazepine. Of the 34 patients who showed a good therapeutic response to unilateral ECT, those taking benzodiazepines had smaller changes in their Hamilton depression ratings from before treatment to after treatment and were more symptomatic at the end of the course of ECT. Thus, when patients take benzodiazepines during a course of unilateral ECT, the maximum therapeutic response may be compromised.*

(Am J Psychiatry 1990; 147:1029–1035)

The purpose of this study was to assess whether patients taking benzodiazepines during a course of ECT (usually, 6–12 treatments) experience a lessening of the therapeutic effects of ECT. Generally, concomitant medications are discouraged, but they may be prescribed for various reasons during a course of ECT (1–3). For example, if the patient has been taking a benzodiazepine for some time, lengthy and difficult tapering of the dose may be required. A patient's severe anxiety and insomnia may also prompt the physician to prescribe benzodiazepine medication during ECT.

Benzodiazepines raise the patient's basal seizure threshold, and elevation of the basal seizure threshold before ECT increases the risk of inefficient administration of the treatment. A patient may be given disproportionate amounts of electrical charge or multiple stimulations to elicit the seizure. If a generalized seizure is successfully induced despite the inefficiency, we still do not know whether benzodiazepines compromise the efficacy of ECT.

Briefer seizures (less than 25–30 seconds) have been documented in patients who were taking benzodiazepines during ECT (3–5). Empirical evidence that this occurrence compromises the therapeutic effectiveness of ECT is lacking. A number of investigators have shown that seizure duration alone does not correlate with therapeutic effectiveness (6–9).

Stromgren et al. (3) reported that on the average, patients given a benzodiazepine-ECT combination required three additional ECTs. This finding was subsequently challenged in the Northwick Park ECT trials (10, p. 1318): "Improvement scores were similar in patients with and without diazepam" when the two groups received comparable amounts of treatment (approximately eight ECTs). (See also Johnstone et al. [11].) The Johnstone et al. study was criticized for not monitoring seizure activity with EEG (12), but this would not necessarily account for the discrepancy in ECT results between that study and the Stromgren et al. study. The different conclusions regarding the use of benzodiazepines were probably due to the difference in electrode placement; Stromgren et al. used unilateral and Johnstone et al. used bilateral placement.

Sackeim et al. (9) found that the therapeutic response to unilateral ECT depended on suprathreshold stimulation, whereas response to bilateral ECT did not. Stimulation *just above* seizure threshold can result in generalized seizures of adequate length (Sackeim et al. reported a mean of 59.6 seconds) without the patient showing any mood improvement. In contrast, marginally suprathreshold stimulations given with bilateral placement resulted in significant mood improvement for the majority of patients. Given that benzodiazepines raise seizure threshold, using a benzodiazepine during unilateral ECT might have negative effects that were never observed when bilateral ECT was so widely used (13).

The present study explored both the efficiency and the effectiveness of unilateral ECT for patients taking benzodiazepines during the course of ECT.

Revised version of a paper presented at the 140th annual meeting of the American Psychiatric Association, Chicago, May 9–14, 1987. Received Aug. 19, 1989; revision received Jan. 30, 1990; accepted March 2, 1990. From the Carrier Foundation. Address reprint requests to Dr. Pettinati, Research Division, Carrier Foundation, Belle Mead, NJ 08502.

Supported by the Carrier Foundation.

The authors thank K. Meyers, A. Ergin, and R. Greenberg for their comments; A. Perr and J. Olesnevich for assisting in administering the ECT and scoring the EEG tracings; and the clinical ECT staff, particularly L. Bedient, J. Glesmann, and M. Tompkins.

## METHOD

The study included 48 inpatients admitted to a private, nonprofit psychiatric hospital for whom unilateral ECT had been ordered by their attending psychiatrists. The hospital's policy is to start with unilateral ECT. Ninety-four percent (N=45) of the patients had diagnoses of major depression and three patients had diagnoses of bipolar disorder, depressed, according to *DSM-III* criteria. Three different psychiatrists who interviewed each patient on separate occasions agreed with the diagnoses of the patients included in this study. Patients who had received ECT within 6 months and/or had an organic mental disorder were excluded.

The 48 patients were grouped according to whether or not they were taking benzodiazepines during the course of ECT. Seventy-one percent (N=34) were in the benzodiazepine group. The proportions of those taking antidepressants or neuroleptics were relatively similar in the benzodiazepine and nonbenzodiazepine groups: 53% (N=18) and 50% (N=7), respectively. Fifty percent (N=7) of the nonbenzodiazepine group were not taking any psychotropic medications.

Of the 34 benzodiazepine patients, 71% (N=24) were taking one benzodiazepine, 26% (N=9) were taking two, and only one patient was taking three. The most commonly prescribed anxiolytic was alprazolam (38%, N=13). Less commonly prescribed were lorazepam (N=7) and clonazepam (N=4). The most commonly used hypnotic was temazepam (29%, N=10). Less commonly prescribed were triazolam (N=5) and flurazepam (N=3). Forty-one percent (N=14) of the benzodiazepine group received benzodiazepines twice, three times, or four times a day during the course of ECT, whereas approximately 29% (N=10) received benzodiazepines for nighttime sleep only.

ECTs were administered every other day, three times a week. The electrodes were placed in one of three nondominant, unilateral temporoparietal positions (14–16). Dominance was evaluated by means of a handedness inventory (14). One of two bipolar brief-pulse, constant-current machines was used: a MECTA SR-1 or a Thymatron (maximum charges of 576 and 504 millicoulombs [mC], respectively). Both the type of unilateral placement and the type of machine had been randomly assigned as part of a separate study. Thirty percent of each placement type and 50% of each machine type was represented in each of the two study groups, benzodiazepine and nonbenzodiazepine. The initial machine parameters for both the MECTA SR-1 and the Thymatron were based on guidelines described in the Thymatron manual (17). We modified these guidelines for use with the SR-1 by increasing the charge by 35 mC for each 5 years of the patient's age (seizure threshold increases with age [9, 18]).

An anesthesiologist or nurse anesthetist induced a light coma intravenously with methohexital sodium, typically, 1.5 mg/kg of body weight; occasionally, thiopental sodium, 3.5 mg/kg of body weight, was substituted when patients tolerated it better than methohexital. The mean methohexital doses for the benzodiazepine and the nonbenzodiazepine groups were 102.9 and 103.6 mg, respectively. This difference was not significant (t=0.17, df=43, n.s., two-tailed test). (Since the time of this study, our average methohexital dose has been lowered to 0.9 mg/kg.) Succinylcholine, 25–100 mg, was given intravenously immediately following the onset of anesthesia.

Seizure length was monitored on a two-lead single-channel EEG using the monitoring system of the MECTA or on an external EEG monitor with the Thymatron. One EEG lead was applied directly above the left eyebrow (midorbit) and one over the left temporal region. Seizure length was measured in seconds by two trained research nurses who independently scored the EEG tracings. The interrater agreement (alpha coefficient) was 0.97 (F=4.1, df=1, 269, p=0.04).

If no seizure occurred (0 seconds according to the EEG criteria), a missed seizure was counted, and immediate restimulation at the same electrical parameters occurred. If seizure activity lasted less than 25 seconds, it was counted as a brief seizure. If the ECT physician and nurse agreed that motor activity had not occurred in the ipsilateral cuffed limb, a focal seizure was counted. For brief and focal seizures, after 30 seconds of oxygenation, the patient was restimulated at higher parameters. In all cases, restimulation was administered without further anesthesia, and no more than three stimulations per treatment session were given.

The severity of depression was assessed with the 24-item Hamilton Rating Scale for Depression (19). For this study, ratings were done twice (evaluations 1 and 2) by a research psychiatric nurse. In evaluation 1, the Hamilton scale was administered 24–48 hours before the patient's first ECT; evaluation 2 took place 24–48 hours after approximately the sixth ECT.

Although the total number of ECTs was determined by the patient's attending psychiatrist, the sixth treatment was selected for the second evaluation, because this allowed for a reasonable assessment of effectiveness at a fixed point in time. For 21% (N=10) of the sample, however, the second evaluation occurred after the fourth or fifth ECT, rather than the sixth, since the attending physician stopped unilateral ECT, either because she or he felt there was sufficient improvement in mood (N=6: 21% [N=3] of the nonbenzodiazepine group and 9% [N=3] of the benzodiazepine group) or, alternatively, because not enough improvement had been observed (N=4) and the patients were switched to bilateral ECT. This latter condition occurred only in the benzodiazepine group.

The percent change in the Hamilton depression ratings from evaluation 1 to evaluation 2 plus the Hamilton score at evaluation 2 were used to classify patients' response to unilateral ECT. That is, a patient classified as a responder after approximately six unilateral ECTs was defined as one who at evaluation 2 had made at least a 30% improvement in depression score since the pretreatment rating and had a depression score of less than 22. These criteria were arbitrarily determined by

**TABLE 1. Characteristics of 48 Patients Who Were or Were Not Taking Benzodiazepines During a Course of ECT**

| Characteristic | Total Sample (N=48) | | | | Benzodiazepine Group (N=34) | | | | Nonbenzodiazepine Group (N=14) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | % | Mean | Range | N | % | Mean | Range | N | % | Mean | Range |
| Female sex | 28 | 58.3 | — | — | 21 | 61.8 | — | — | 7 | 50.0 | — | — |
| Age (years) | — | — | 62.3 | 28–85 | — | — | 61.2 | 28–79 | — | — | 65.1 | 35–85 |
| Age at onset of illness (years) | — | — | 49.4 | 19–79 | — | — | 48.1 | 19–79 | — | — | 51.8 | 27–76 |
| Melancholic illness | 27 | 56.3 | — | — | 22 | 64.7 | — | — | 5 | 35.7 | — | — |
| Recurrent illness | 38 | 79.2 | — | — | 26 | 76.5 | — | — | 12 | 85.7 | — | — |
| Prior ECT | 19 | 39.5 | — | — | 12 | 35.2 | — | — | 7 | 50.0 | — | — |

modifying those that Sackeim et al. (20) reported for a full treatment course: change of 60% in Hamilton score and a score of 16 or less. (We are not aware of published criteria for evaluating improvement through Hamilton depression ratings before the end of the treatment course.) While 13 of 34 responders at evaluation 2 had a change in depression score of less than 60%, 10 of the 13 had a depression score of 16 or less. Also, at evaluation 2, ECT responders as a group had a mean±SD change in score of 69.9%±20.6% and a mean score of 8.1±5.7, whereas ECT nonresponders had a change of 12.2%±27.8% and a score of 28.1±8.7 (responders versus nonresponders: for change in score, $t=7.0$, $df=46$, $p<0.0001$, two-tailed test; for score at evaluation 2, $t=7.9$, $df=46$, $p<0.001$, two-tailed test).

## RESULTS

Table 1 displays some of the key demographic characteristics for the total sample and for the benzodiazepine and nonbenzodiazepine groups. There were some interesting trends, although there were no statistically significant differences between groups. Failure to find statistical differences was probably due, in some cases, to small subgroup sizes. While the nonbenzodiazepine group tended to have a lower rate of melancholia, they were older, a greater proportion were male (50% versus 38%), they had a higher rate of recurrent depression, they were older at first onset of illness, and a greater proportion had had prior ECT.

### *Efficiency of Unilateral ECT With Benzodiazepines*

The mean±SD initial stimulus settings across treatment for the 48 patients were as follows for the MECTA SR-1 and Thymatron combined: frequency=76.7±7.6 Hz, pulse width=1.5±0.4 msec, and duration=2.18±0.85 seconds. There were no statistical differences on any of the electrical stimulus parameters between the benzodiazepine and the nonbenzodiazepine groups.

The mean±SD total number of unilateral ECTs for the sample was 6.7±1.9 (range=4–13). When the bilateral ECTs were included, the mean total number of treatments was 8.2±2.5 (range=4–14). The mean number of bilateral ECTs for only the patients who had been switched was 4.2±2.0. The mean total numbers of unilateral ECTs were almost identical for the benzodiazepine and nonbenzodiazepine groups: 6.8±1.95 and 6.6±1.70, respectively.

The mean±SD total number of unilateral stimulations (i.e., initial stimulation plus any restimulations) was 9.1±3.7 (range=4–24). Although the difference was not statistically significant, the benzodiazepine group required an average of one more unilateral stimulation than the nonbenzodiazepine group: mean=9.5 (range=4–24) and mean=8.1 (range=6–12), respectively ($t=1.5$, $df=46$, n.s., two-tailed test).

Of six patients who had at least one missed seizure during unilateral ECT, five (83%) were in the benzodiazepine group; of seven patients who had at least one focal seizure during unilateral ECT, 6 (86%) were in the benzodiazepine group; and of 25 patients who had at least one brief seizure during unilateral ECT, 20 (80%) were in the benzodiazepine group. The mean±SD seizure duration per treatment, when calculated across cumulative restimulations per treatment, was similar in the benzodiazepine and the nonbenzodiazepine groups: 37.5±16.4 seconds and 39.6±12.8 seconds, respectively ($t=0.45$, $df=46$, n.s., two-tailed test).

The mean±SD charge delivered per stimulation was 19.5±11.2 mC per stimulation more in the nonbenzodiazepine than in the benzodiazepine group: 401.8±103.4 mC per stimulation versus 390.6±128.5 mC per stimulation. Although this difference was not statistically significant ($t=0.29$, $df=46$, n.s., two-tailed test), the amount of total charge delivered per stimulation was covaried in all subsequent analyses. A difference in charge between groups was anticipated because of the slightly greater mean age of the nonbenzodiazepine group, since initial electrical stimulus parameters are higher for older patients (21). To assess whether the better response of the nonbenzodiazepine group was mediated by the additional electrical charge, six elderly patients (mean age=71.3 years) were randomly selected from the benzodiazepine group, and six (mean age=73.5 years) were then selected from the nonbenzodiazepine group by age matching. In these two subgroups the relation between effectiveness of treatment and charge was actually in the opposite direction from that which would be anticipated if charge were the

mediating variable: the benzodiazepine group, by evaluation 2, had received a slightly higher mean charge and yet showed a smaller mean change in Hamilton depression score than the nonbenzodiazepine group: 491.8±66.4 mC per stimulation with a 58.5%±4.4% change in score and 476.2±63.7 mC per stimulation with an 88.7%±9.0% change in score, respectively.

*Effectiveness of Unilateral ECT With Benzodiazepines*

To assess the potential interaction between benzodiazepines and unilateral ECT as related to the therapeutic effectiveness of ECT in treating depression, the following assessments were made: 1) the proportions of patients defined as responders and nonresponders who were taking benzodiazepines and 2) the extent of therapeutic change in ECT responders (evaluated by comparing the changes in their depression ratings from evaluation 1 to evaluation 2).

For the total sample, the mean±SD Hamilton depression ratings at evaluation 1 and evaluation 2 were 30.0±9.6 and 14.0±11.3, respectively; the mean change in rating between the two evaluations was 53.0%±34.8%. Overall, unilateral ECT resulted in considerable improvement in mood for the majority of this sample. The pretreatment (evaluation 1) depression scores were not statistically different for the benzodiazepine and the nonbenzodiazepine groups: mean±SD=30.8±5.6 and 29.7±10.8, respectively (t=0.47, df=46, n.s., two-tailed test), nor did the pretreatment depression ratings differ statistically for the responders and the nonresponders: 28.5±8.0 and 33.6±12.1, respectively (t=1.4, df=46, n.s., two-tailed test).

At evaluation 2, of the 14 patients in the nonbenzodiazepine group, 93% (N=13) were ECT responders, whereas only 62% (N=21) of the 34 benzodiazepine patients were ECT responders (p=0.03, Fisher's exact test). This finding indicated a relationship between taking a benzodiazepine and not responding to unilateral ECT.

Of the 14 ECT nonresponders at evaluation 2, 11 were switched to bilateral ECT. Of these, 82% (N=9) responded to a mean±SD of 5.3±1.8 bilateral ECTs. For these nine bilateral ECT responders, the mean±SD Hamilton depression rating was 6.3±9.9 following their final bilateral ECT; their change in score from pretreatment was 80.3%±3.8%. This is a remarkable response to bilateral ECT after a change of only 16.3%±5.1% following the initial five or six unilateral ECTs. The final mean depression score of the ECT nonresponders who were *not* switched to bilateral ECT was 26.5±8.5. The response that was finally seen with bilateral ECT argues against the explanation that the group taking benzodiazepines may have had a clinical profile that would profit relatively little from ECT. These data also suggest that the effectiveness of bilateral ECT was not compromised by using benzodiazepines. Obviously, firm conclusions about whether benzodiazepines affect bilateral ECT cannot be drawn from this study. A randomized design in which benzodiazepine patients are assigned to unilateral versus bilateral ECT must be used.

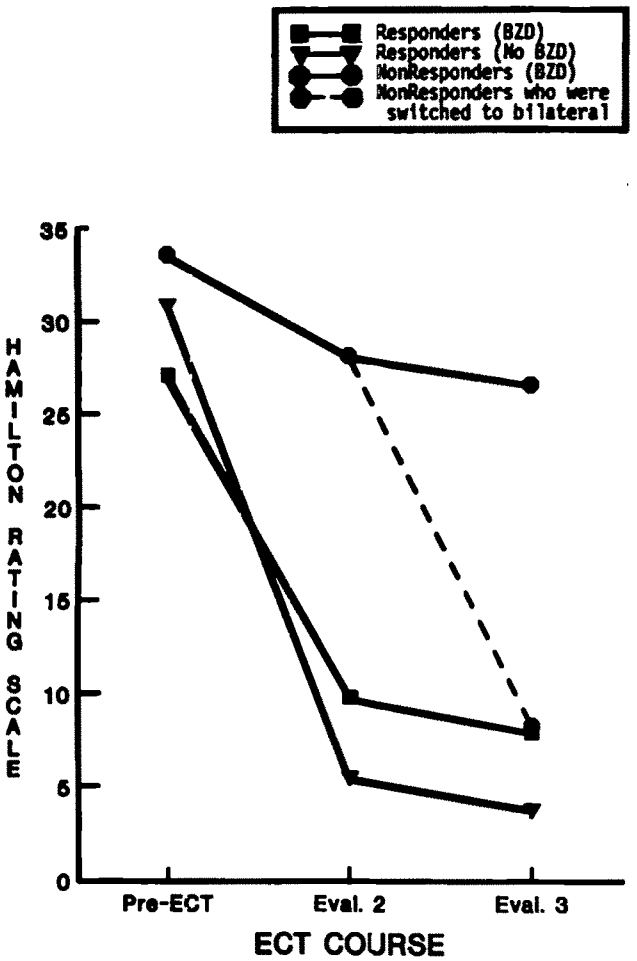
To assess whether the change in Hamilton depression score for unilateral ECT responders at the second evaluation was different for those taking benzodiazepines, we compared the change in ratings from evaluation 1 to evaluation 2 *for responders only* in the benzodiazepine and nonbenzodiazepine groups. A one-way analysis of covariance (ANCOVA; two covariates) was conducted on the depression rating at evaluation 2 for the benzodiazepine and the nonbenzodiazepine ECT responder groups, covarying the pretreatment depression rating and the amount of electrical charge per stimulation. (Age was not added as a third covariate because it was highly correlated with charge in this sample. When a second ANCOVA was performed with age as a second covariate instead of charge, the two ANCOVAs yielded similar results.)

The analyses revealed that the nonbenzodiazepine group who had responded to unilateral ECT by evaluation 2 had a nearly asymptomatic mean Hamilton depression rating of 5.5±4.8, which was significantly smaller than the rating of 9.8±5.7 found in the benzodiazepine ECT responder group (F=6.9, df=3, 30, p=0.01). Thus, the nonbenzodiazepine responder to unilateral ECT made a significantly better recovery than the benzodiazepine responder: the changes in depression score were 81.0%±16.6% and 62.9%±19.9%, respectively (F=7.6, df=3, 30, p=0.01).

Figure 1 demonstrates this relationship between the mean Hamilton depression ratings at evaluations 1 and 2 for the 34 responders and the 14 nonresponders and whether or not they were taking benzodiazepines. A third Hamilton depression rating is also shown. This rating was obtained within 48 hours after the final ECT when ECTs had continued past evaluation 2. (The raters and procedures were the same as those used in obtaining the previous depression ratings.) For one-third of the sample, the evaluation 3 depression rating was the evaluation 2 rating, since evaluation 2 had followed their last ECT. Given this repeated data point from evaluation 2 to evaluation 3, the statistical analyses in this article could not include evaluation 3 depression ratings.

Medication-related variables were examined in relation to the results of this study. Overall, there was not an obvious relationship, although any conclusion should be viewed as preliminary, given the low statistical power in analyses using the following subgroups. There was a trend for the 10 patients who were taking more than one benzodiazepine to be more represented in the group who responded to ECT: 33% (N=7) of the responders, compared with 23% (N=3) of the nonresponders (p=0.40, n.s., Fisher's exact test). Alprazolam was taken by a greater percentage of those who did not respond to ECT: 46% (N=6) of the

**FIGURE 1. Change Over a Course of ECT in Mean Scores on the Hamilton Rating Scale for Depression of Responders and Nonresponders With Regard to Concomitant Benzodiazepine (BZD) Use**




nonresponders, compared with 33% (N=7) of the responders (p=0.35, n.s., Fisher's exact test). Temazepam was less represented among the patients who responded to ECT: 29% (N=6) of the responders, compared with 33% (N=4) of the nonresponders (p=0.41, n.s., Fisher's exact test). The proportion of patients taking daily doses of benzodiazepines was larger (but not significantly so) among those who responded to ECT; 48% (N=10) of the responders, compared with 31% (N=4) of the nonresponders (p=0.27, n.s., Fisher's exact test). There was no difference between responders and nonresponders in the proportions of patients taking benzodiazepines for nighttime medication only: 29% (N=6) and 31% (N=4), respectively (p=0.59, n.s., Fisher's exact test). Therefore, no discernible relationship could be observed between response to ECT and 1) taking more than one benzodiazepine, 2) taking a specific type of benzodiazepine, 3) dosage and frequency of administration, and 4) whether a benzodiazepine was given only for sedation at night.

## DISCUSSION

The primary results of the comparison of ECT patients who were and were not taking benzodiazepines were the following. 1) A significant proportion of patients taking benzodiazepines did not respond to unilateral ECT (compared with response in the nonbenzodiazepine group). Importantly, 82% of these unilateral ECT nonresponders showed a dramatic therapeutic response when given approximately five bilateral ECTs. 2) Significantly less improvement in depressive symptoms (more remaining dysphoric symptoms) was observed in unilateral ECT responders who had been taking benzodiazepines during the course of ECT than in the unilateral ECT responders who were not taking benzodiazepines.

Theoretically, it would be important to establish how the reduced therapeutic effect seen in this sample was related to the concomitant use of benzodiazepines and ECT. Gulati et al. (22) reported that the up-regulation of brain benzodiazepine receptors by electroconvulsive shock in rats may potentiate benzodiazepines' anticonvulsant properties (see also 23, 24). On the basis of a study of male mice, Green and Mountford (25) suggested that benzodiazepines may interfere with postictal mechanisms which are involved in initiating the eventual alterations of monoamine-mediated behavioral responses (see also 26).

Even though improvement in mood has been associated with alprazolam (27), some patients experience increased depressive symptoms when taking benzodiazepines (28, 29). However, 82% of the unilateral ECT nonresponders who were switched to bilateral ECT in our study showed a dramatic improvement in mood after they had received an average of five bilateral ECTs. It cannot be determined whether these nonresponders would have shown a similar response had they continued with unilateral treatments. The dramatic improvement following the switch to bilateral ECT weakens the argument that the benzodiazepine-ECT interaction responsible for reduced effectiveness of ECT is a pharmacodynamic one. One might then postulate that the therapeutic neurochemical mechanisms involved in unilateral and bilateral ECT are different.

A more plausible explanation for our data is that the differential therapeutic response to unilateral and bilateral ECT means that patients may have been stimulated barely above their seizure thresholds (9). At first glance, this may seem unlikely, given that the average electrical charge for this sample was in the upper range of available charges in comparison with those reported by Sackeim et al. (20). However, our sample, as a group, would have had a much higher threshold than that of Sackeim et al.'s subjects because of the higher methohexital doses and benzodiazepine use. Collectively, these factors can make it more difficult to give suprathreshold stimulations with the ECT devices that are presently available.

While benzodiazepine use is more easily altered than

endogenous factors associated with high seizure thresholds, such as greater age and male sex (18, 20, 30), it may be reasonable to investigate artificially lowering the seizure threshold (for example, by pretreating with intravenous caffeine benzoate [31, 32]). Also, certain antidepressants taken during ECT could lower seizure threshold, thereby potentiating unilateral ECT. (The earlier literature has not reported a potentiating effect of antidepressants on the effectiveness of ECT [33], but most of the earlier studies used bilateral ECT.)

Unfortunately, standard clinical ECT practice does not determine how much energy above a patient's seizure threshold is required for a therapeutic generalized seizure. However, we speculate that if the electrical charge given to each patient in this study had been suprathreshold, unilateral ECT might have been as efficacious as bilateral ECT for the nonresponders who were switched and responded to bilateral ECT.

Suprathreshold stimulation was ensured in a study in which nondominant, unilateral ECT was given to treatment-resistant manic patients (34). In that study Mukherjee et al. electrically stimulated patients 150% above their initial seizure thresholds, which were determined by titrating their first electrical doses. It was found that unilateral ECT was as efficacious as bilateral ECT in 50% of the manic patients. This finding conflicted with a previous report by Small et al. (35) which indicated that unilateral ECT was not useful for manic patients. Interestingly, Small et al. reported that a benzodiazepine as needed for bedtime sedation had been used more frequently in the manic patients receiving unilateral ECT who had subsequently been switched to bilateral ECT (p. 129). Small and colleagues later reported on drug-free, manic patients who still did not improve with unilateral ECT (36). The stimulus parameters they used were the usual clinical settings and were not predicated on each individual's seizure threshold.

## CONCLUSIONS

We feel that our findings have theoretical and practical importance for defining applications in the clinical setting, although we acknowledge that caution is necessary in drawing conclusions derived from a nonrandomized, retrospective study. In particular, our results show that use of benzodiazepines may impede the full therapeutic effect of unilateral ECT. Our study underscores the need to discontinue benzodiazepines before unilateral ECT is given. In addition, we also recognize that the practice of discontinuing benzodiazepines is clinically impractical for some patients, making it imperative to consider alternative ECT procedures. The effectiveness of unilateral ECT has been heatedly debated for almost 30 years. Progress in resolving this issue is more likely now because the focus is on identifying those conditions under which unilateral ECT may be at a disadvantage and those which optimize its benefits.

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# The Role of Depression in Couples Involved in Murder-Suicide and Homicide

Milton Rosenbaum, M.D.

*Twelve couples in cases of murder-suicide were compared to 24 couples in cases of homicide during the period 1978 to 1987 in Albuquerque, N.M. Data were obtained from police, the courts, hospital records, and interviews with friends and family of the deceased. The most striking findings were that perpetrators of murder-suicide were depressed (75%) and men (95%), while perpetrators of homicide were not depressed and one-half were women. The data indicate that the murder-suicide and homicide groups are two different populations.*

(Am J Psychiatry 1990; 147:1036–1039)

Rosenbaum and Bennett (1) have reported that depressed patients with homicidal potential differ from nonhomicidal depressed patients. Homicidally depressed patients are more likely to have a personality disorder, to abuse alcohol, to be physically abusive, and to have had a chaotic childhood. However, in that study there were homicidal threats and attempts but no homicide. Therefore, I decided to study cases of domestic homicide (murder of family members or intimates). This report is concerned with a comparison of cases of couples in which there was murder followed by suicide and those in which there was homicide.

Murder followed by suicide is relatively rare. In the United States the rate is about 0.22 per 100,000 population (2). The rates in Europe are similar. However, the percentage of murder-suicide among all homicides varies from 2% in North Carolina to 33% and 42% in England and Denmark, respectively (3). More will be said about this in the Discussion. During the period 1978–1987 in Albuquerque, 20% of the domestic murders involved murder-suicide.

The psychiatric and other medical literature on murder-suicide is sparse. The primary reason is that most investigations of murder-suicide are done by police, coroners, or the courts, and there is little or no input from psychiatric and other medical personnel. In addition, both perpetrator and victim are dead, and, therefore, in contrast to cases of homicide, there is no trial, no public concern, and, most importantly, little or no concern by medical and psychiatric personnel. The exception is when the perpetrator or victim is well-known, as in the case of the murder-suicide of the Pulitzer Prize-winning reporter for the *Chicago Herald Tribune* and his wife in 1980 (4).

With few exceptions, the reports are demographic or consist of a few cases gathered from police and/or coroner files, and there are no data from personal contact with family or friends (5, 6). By far, the most definitive study of murder followed by suicide is that by West (7). His data came from police and coroner files, and further reports were sought from doctors, social workers, and hospitals. However, for "ethical reasons," family members, relatives, and friends were not contacted. In his study, the most prevalent psychiatric disorder among the perpetrators was depression.

## METHOD

The clinical material came from the files of the Albuquerque Police Department for the 10-year period 1978–1987. In the cases of homicide, additional information (including the court records) came from the files of the district attorney of Bernalillo County.

There were 17 cases of murder followed by suicide in this period. Of those 17, 12 involved couples. During the same period there were 24 cases of domestic homicide involving couples.

In the 12 cases of murder followed by suicide, further data were obtained from hospital records in four cases and by telephone and/or personal interviews with family members, relatives, and friends of the deceased in all 12 cases. To the best of my knowledge, this is the largest series of murder-suicide cases in which such data have been gathered.

In the cases of murder without suicide, the court records included police reports; pretrial, trial, and posttrial reports; and, in 14 cases, detailed psychological reports on the murderers by court-affiliated psychologists. Further data were obtained by telephone

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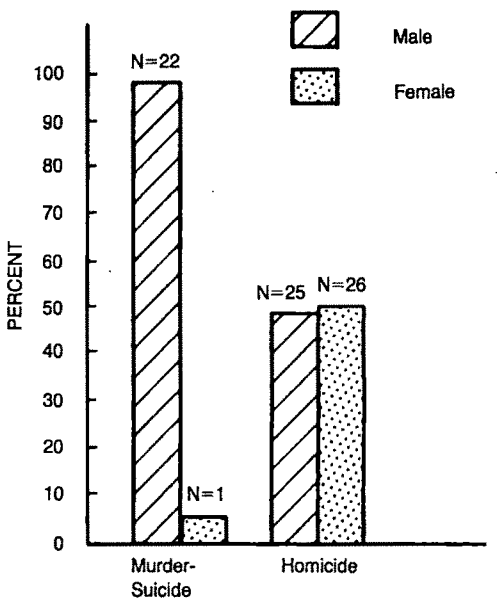
The author thanks Dr. Robert Lorch and Dr. Betty Skipper for their help with statistical analysis.

**TABLE 1. Diagnosis of Perpetrators and Victims in Cases of Murder-Suicide and Homicide Involving Couples**

| | Perpetrators | | | | Victims | | | |
|---|---|---|---|---|---|---|---|---|
| | Murder-Suicide (N=12) | | Homicide (N=24) | | Murder-Suicide (N=12) | | Homicide (N=24) | |
| Diagnosis[a] | N | % | N | % | N | % | N | % |
| Axis I | | | | | | | | |
| Depressive disorder[b] | 9 | 75 | 0 | 0 | 0 | 0 | 0 | 0 |
| Psychoactive substance abuse | 2 | 17 | 12 | 50 | 1 | 8 | 10 | 42 |
| Adjustment disorder | 1 | 8 | 5 | 21 | 0 | 0 | 3 | 12 |
| Delusional disorder | 0 | 0 | 2 | 8 | 0 | 0 | 0 | 0 |
| None[c] | 0 | 0 | 5 | 21 | 11 | 92 | 11 | 46 |
| Axis II | | | | | | | | |
| Antisocial personality disorder[d] | 4 | 33 | 16 | 67 | 1 | 8 | 14 | 58 |
| Other personality disorder | 0 | 0 | 4 | 17 | 0 | 0 | 4 | 17 |
| None[e] | 8 | 67 | 4 | 17 | 11 | 92 | 6 | 25 |

[a]According to *DSM-III-R*.
[b]Includes major depression (N=6), bipolar disorder (N=2), and dysthymia (N=1). Significant difference between perpetrators of murder-suicide and homicide ($p<0.001$, Fisher's exact test for all comparisons).
[c]Significant difference between victims of murder-suicide and homicide ($p<0.05$).
[d]Significant difference between victims of murder-suicide and homicide ($p<0.01$).
[e]Significant differences between perpetrators of murder-suicide and homicide ($p<0.01$) and victims of murder-suicide and homicide ($p<0.01$).

**FIGURE 1. Sex of Perpetrators in Two Studies of Murder-Suicide and Homicide Involving Couples[a]**




[a]For the murder-suicide group, data on 12 perpetrators are from the present study and data on 11 perpetrators are from an article in *Time* (8); for the homicide group the numbers are 24 and 27, respectively. Twenty-two perpetrators of murder-suicide were men, and only one was a woman ($p<0.001$, Fisher's exact test).

interviews with relatives and family members in six cases and by review of hospital records in four cases.

The article "7 Deadly Days" (8) contained vignettes of 464 people who died by gunfire in the United States in the week of May 1–7, 1989. Data were obtained from the cases of 11 couples involved in murder-suicide and 27 couples involved in homicide.

The two-tailed t test was used to compare mean ages; Fisher's exact test was used for all other statistical analyses.

## RESULTS

The most significant findings are given in table 1 and figure 1. Most of the perpetrators of murder-suicide were men; half of the perpetrators of homicide were men. Perpetrators of murder-suicide were older than perpetrators of homicide (mean±SD age=42.3±14.2 versus 33.4±9.1; $t=2.38$, $df=34$, $p<0.05$); there was no difference in age between victims of murder-suicide and homicide (34.7±11.2 versus 33.4±8.5; $t=0.39$, $df=34$, n.s.). Six perpetrators of murder-suicide were Hispanic, and six were non-Hispanic white. Eleven perpetrators of homicide were Hispanic, eight were black, four were non-Hispanic white, and one was Native American ($p<0.05$). Five victims of murder-suicide were Hispanic, and seven were non-Hispanic white. Nine homicide victims were Hispanic, ten were non-Hispanic white, and five were black. Couples involved in murder-suicide were of higher socioeconomic class than couples involved in homicide (ratings of 8 versus 6; $p<0.05$).

Eight couples in the murder-suicide group were married (average of 15 years), compared to six in the homicide group (average of 6 years) ($p<0.05$). At the time of the crime, eight couples in the murder-suicide group, compared to two couples in the homicide group, were separated ($p<0.001$).

The relationships were chaotic; there was physical abuse in seven of the couples involved in murder-suicide and in 21 of the couples involved in homicide. All male perpetrators in both groups were extremely jealous of their partners.

Alcohol and drug abuse was more common in perpetrators and victims of homicide than murder-suicide (12 perpetrators and 12 victims versus four perpetrators and one victim; $p<0.05$). Drinking at the time of the crime was also more common in perpetrators and victims of homicide than murder-suicide (12 perpetrators and nine victims versus four perpetrators and no victims; $p<0.05$).

*Case 1.* A 55-year-old white man married for 30 years shot and killed his 50-year-old wife and then killed himself. He

was a successful salesman, was a heavy drinker, and had not worked for 3 months because he was depressed. There were marital problems, including physical abuse and two previous brief separations. He was extremely jealous of his wife and accused her of having an affair. About a year before the tragedy, his wife got a job, which she enjoyed. She was planning to leave her husband because he refused to seek psychiatric help. On the day of the tragedy he was drinking, and a violent quarrel was followed by the murder-suicide.

*Case 2.* A 25-year-old black woman had lived with a 25-year-old black pimp for a year. There was much arguing, fighting, and drinking. One night, because he needed money, he asked her to go out on the street for him. She refused, he hit her, and she ran into a room and locked the door. He said, "I'm going to kick your ass—if you have the gun, you'd better use it." He kicked the door open, and she shot and killed him. Both had been drinking, and both had police records. She had refused to work as a prostitute for him and was trying to leave him.

## DISCUSSION

The two most striking findings are the diagnostic and sex differences between the two groups. In the murder-suicide group, the large majority of perpetrators (75%; eight men, one woman) suffered from depression; none of the perpetrators in the homicide group suffered from depression. None of the 11 women victims in the murder-suicide group had gross psychopathology; however, most of the victims in the homicide group, both men and women, were characterized by substance abuse, personality disorder, and sociopathology (table 1).

In the 24 cases of homicide, 12 of the perpetrators were women, and in the 12 cases of murder-suicide, 11 of the perpetrators were men and one was a woman; this difference was significant ($p<0.05$). The data from *Time* corroborate these findings. In the 11 cases of murder-suicide all of the perpetrators were men, while in the 27 cases of homicide 13 of the perpetrators were men and 14 were women ($p<0.01$) (figure 1).

The murder-suicide group, which consisted primarily of middle-socioeconomic class non-Hispanic whites and Hispanics, was characterized by depressive illness with personality disorder in the male perpetrator, "normal" female victims, a relatively long-term relationship, and separation at the time of the crime. The homicide group, which consisted primarily of lower-socioeconomic class blacks and Hispanics, was characterized by personality disorder, substance abuse, and antisocial behavior in both perpetrators and victims; a relatively brief relationship; and cohabitation but threatened separation at the time of the crime. One-half of the women victims of murder-suicide were in the process of liberating themselves and undergoing personal growth (returning to school, getting a job, and advancing in their work).

In view of the small proportion of blacks in Albuquerque (about 2%), it was striking that one-third of the perpetrators in the homicide group were black (N=8) and that there were no blacks in the murder-suicide group. It is well-known that the rate of homicide among blacks is high. In Albuquerque, the rate is 77.2 per 100,000, which is 10 times that of the non-Hispanic white population and five times that of Hispanics. Perhaps the high number of women among the black perpetrators (five of eight) reflects the matriarchal aspect of black society, in which women are both dominant and aggressive. Unlike the women in the murder-suicide group, they "got rid" of the man. In addition, the men in the homicide group did not commit suicide; rather, they taunted ("you don't have the guts to shoot that gun") and provoked the women to kill them. The data from *Time* are similar. Of the 23 cases of homicide in which race could be identified, 13 of the perpetrators were black, and eight of these were women. In comparison, in the 11 cases of murder-suicide, two of the perpetrators were black, and they were men. A most striking finding in the homicide group was that the five black women all killed black men (four lovers and one ex-husband), while the three black men did not kill black women, but rather two non-Hispanic white women and one Hispanic woman.

In an interesting study of the epidemiology of homicide and murder followed by suicide in a variety of countries, Coid (3) found that the higher the rate of homicide in a population, the lower the percentage of murder-suicide. Thus, in the United States, which has a homicide rate of 10 per 100,000, the percentage of murder-suicide is 4%, while in Denmark, which has a very low homicide rate, it is 42%. However, the rate of murder-suicide remains the same (range=0.21–0.27 per 100,000) despite wide differences in the homicide rate. In Albuquerque, the homicide rate is 12 per 100,000 and the percentage of murder-suicide is 4%, but the murder-suicide rate is 0.25 per 100,000. Coid suggested that such a constancy may reflect the constancy of mental illness in various population groups. In cases of murder followed by suicide, the mental illness is usually depression.

The findings from the present study suggest that patients with the following features may be at risk for murder-suicide: depression, male gender, and married or living with a woman in a long-term relationship characterized by discord, physical abuse, and frequent separations and reunions. Furthermore, men at risk for murder-suicide are likely to abuse alcohol, have a history of violent behavior and previous depressive episodes, and have a longstanding personality disorder. The most important feature is the presence of morbid jealousy. West said, "The greatest risk of murder-suicide would occur in paranoids . . . especially those in whom the emotional distress takes a depressive form" (7).

The onset of the depression is associated with the breakup of the relationship when the woman leaves. The tragedy is triggered when she tells the man that she is leaving for good or that she has a lover. The final confrontation with severe verbal and physical violence,

often abetted by alcohol, then explosively erupts in murder, which is quickly followed by suicide. From a psychodynamic point of view, the depression may be viewed as a defense against the underlying aggressive and murderous impulses. However, if the "trigger" incident produces intense enough aggressive impulses, the depressive defense is breached and the "murderous impulse" is released. The perpetrator's immediate realization that he or she has committed the crime leads to intense guilt, return of the depressive defense, and suicide. Campbell noted that "in depression there may be episodes of destructive fervor during which ideas of jealousy and retaliation may be acted upon impulsively" (9).

The psychoanalytic concept of suicide as aggression turned against the self is well-known and accepted by psychiatric clinicians. However, the possibility that the intense aggression may result in murder-suicide appears to be not so well-known.

In the present study, three (25%) of the 12 instigators of murder-suicide were in treatment (counseling) at the time of the tragedy. Therefore, the most important factor in the prevention of murder followed by suicide is the clinician's awareness of the homicidal potential in depressed patients, especially in those at risk for murder followed by suicide. This awareness may also prevent malpractice suits (4).

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# A Comparison of Manual and MEDLARS Reviews of the Literature on Consultation-Liaison Psychiatry

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*A systematic manual search for articles related to consultation-liaison psychiatry was compared to a computerized search of the same journals during the same period that was done with the Medical Literature Analysis and Retrieval System (MEDLARS). More articles were located with the manual method (94%) than with MEDLARS (65%).*

(Am J Psychiatry 1990; 147:1040–1042)

The review article is an essential tool for the modern medical researcher. Faced with a vast and ever-growing quantity of scientific data and the need to follow research in a wide variety of disciplines, the clinical scholar uses reviews as a time-saving source of information. In an optimal research review, studies on a clearly defined topic of research are methodically identified, summarized, and compared, and future directions for research are discussed (1).

Given the influence of review articles on research progress, it is critical that the selection of articles to be reviewed not be skewed by author preference. This is particularly important for meta-analysis, in which the data from a number of studies are pooled. The author must make an objective and reproducible search of the scientific literature. One strategy that review authors commonly use to avoid selection bias is to carry out a computer-assisted search using the Medical Literature Analysis and Retrieval System (MEDLARS) or other computerized system for searching the medical literature.

Although a computerized search using key words to define the research topic seems to be an exhaustive and nonbiased time-saving approach to combing the research literature, studies have found evidence to the contrary. DeNeef (2) performed a series of MEDLARS searches for articles on nosocomial streptococcal infections and found that no search identified more than 89% of a designated bibliography of 38 relevant articles. However, that study was limited in its conclusions because the sample of bibliography articles was subjectively selected by the author rather than determined by an exhaustive search of all the articles published on the topic.

Several researchers have compared MEDLARS searches for reports of controlled clinical trials with both comprehensive manual searches and the Register of Controlled Trials in Perinatal Medicine (3–5). Those investigators found identification rates ranging from 29% to 79%, depending on the specific area of research, the approach used to carry out the search, and the experience of the researcher.

Given the apparent limitations in the specificity of computerized searches in the few studies thus far undertaken, there seemed to be a need for a similar comparison in the psychiatric literature. Therefore, we carried out a MEDLARS search to locate articles relating to consultation-liaison psychiatry and compared its specificity with that of a systematic manual search of the same literature.

## METHOD

We manually reviewed all the issues of four psychiatric journals published between 1981 and 1985 and identified all the articles on consultation-liaison psychiatry. The journals were *General Hospital Psychiatry*, *Psychosomatics*, *American Journal of Psychiatry*, and *Archives of General Psychiatry*. These four journals were selected because two represented general psychiatric interests and two were subspecialty journals with a consultation-liaison focus.

The articles were checked for references to consultation-liaison psychiatry by reviewing 1) titles, 2) abstracts, 3) introductions, and 4) methods sections. The manual review was carried out in chronological order for each journal.

Studies were designated as consultation-liaison studies on the basis of specific predetermined criteria. Included were any studies of mental health services provided by consultation-liaison psychiatrists in a setting in which they had to work with medical/surgical personnel or provide care in a medical setting. Studies

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The views expressed in this paper are those of the authors and do not necessarily reflect those of NIMH.

**TABLE 1. Success Rates of Manual and MEDLARS Searches of Four Psychiatric Journals for Articles on Consultation-Liaison Psychiatry Published in 1981–1985**

| Journal | Consultation-Liaison Articles Located | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Number Found by Either Search | Manual Search | | MEDLARS Search | | Both Searches | | MEDLARS but Not Manual | |
| | | N | % | N | % | N | % | N | % |
| *General Hospital Psychiatry* | 90 | 83 | 92 | 65 | 72 | 58 | 64 | 7 | 8 |
| *Psychosomatics* | 89 | 85 | 96 | 54 | 61 | 50 | 56 | 4 | 4 |
| *American Journal of Psychiatry* | 27 | 27 | 100 | 15 | 56 | 15 | 56 | 0 | 0 |
| *Archives of General Psychiatry* | 8 | 7 | 88 | 5 | 63 | 4 | 50 | 1 | 13 |
| Total | 214 | 202 | 94 | 139 | 65 | 127 | 59 | 12 | 6 |

were excluded if they examined 1) the training of consultation-liaison psychiatrists, 2) emergency room consultation, 3) services given by a multidisciplinary primary care team, 4) services that were part of a routine workup of all patients in the setting, 5) patients initially seen by the consultation-liaison service but sent to the psychiatric ward.

After the manual review was conducted, a MEDLARS search was completed for the same four journals and time period. The three key phrases or words used in the review were "consultation-liaison," "consultation," and "general hospital psychiatry." Articles are added to the MEDLARS data base by technicians who assign key words to each article and enter the codes for those key words.

## RESULTS

The success rates of the manual and MEDLARS searches for each journal are presented in table 1. The success rate was calculated as the number of articles located by each search divided by the total number of articles located by both searches. The MEDLARS search had a lower success rate than the systematic method (65% versus 94%). Of the total number of articles identified, only 59% were located by both methods.

The manual method had the highest success rate (100%) in the *American Journal of Psychiatry* and the lowest success rate (88%) in the *Archives of General Psychiatry*. The MEDLARS search did not have a success rate higher than 72% for any journal. The percentage of consultation-liaison articles located with both methods ranged from a high of 64% in *General Hospital Psychiatry* to a low of 50% in *Archives of General Psychiatry*.

The primary reason for missed articles in the manual analysis appeared to be reviewer fatigue. For the 1981 journals the manual review success rate was 100%, but it declined steadily to 88% for the final year reviewed.

The majority of omissions in the MEDLARS search appear to result from conceptual and semantic variations in the field that may have interfered with the technicians' ability to identify key words. For example, the term "ombudsman rounds" comes from the consultation-liaison field, but a technician might fail to associate it with consultation-liaison.

## DISCUSSION

The results of this study suggest that the range of success rates for computerized literature searches on topics in psychiatry is similar to rates previously observed in other medical fields. The manual search used in this study was markedly more successful in locating consultation-liaison articles in psychiatry than was the computerized search. The broad search terms used in the MEDLARS search located only 65% of the articles that were retrieved with both methods. This finding suggests that when MEDLARS searches are used to locate studies on specific research topics in psychiatry, many studies are missed. Therefore, review articles based on only MEDLARS searches of the psychiatric literature may neglect a significant proportion of the articles that have been published, even in major journals, on the topic in question and thus quite likely do not present the full range of research results on that topic.

Clearly, manual reviews are not perfect. Fatigue or boredom appeared to play an important role in the omission of relevant articles in our manual search. If a large number of journals are reviewed in a relatively short time, techniques to minimize this threat (e.g., use of multiple reviewers) should be considered.

The results of the present study suggest that author-defined key words might enhance success rates in computerized literature searches. This addition would decrease the conceptual and semantic confusion of technicians who are unfamiliar with the article or the field of inquiry.

In light of these findings, authors of review articles in psychiatry should be aware that computerized literature searches such as MEDLARS are neither completely accurate nor exhaustive. A manual search in addition can provide a much more accurate body of studies to be reviewed. However, the manual method is more costly and time-consuming than the computerized method and is limited to preselected journals.

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# Validity of the Personality Diagnostic Questionnaire—Revised: Comparison With Two Structured Interviews

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*The authors gave the self-report Personality Diagnostic Questionnaire—Revised (PDQ-R) to 87 applicants for inpatient treatment of severe personality psychopathology and, blind to these results, diagnosed personality disorders in the applicants by using the Personality Disorder Examination and the Structured Clinical Interview for DSM-III-R Personality Disorders. The PDQ-R was not a substitute for a structured interview assessment of axis II disorders because many of its diagnoses were false positives. Its high sensitivity and moderate specificity for most of the axis II disorders suggest, however, that it is an efficient instrument for screening patients with* DSM-III-R *personality disorders.*

(Am J Psychiatry 1990; 147:1043–1048)

As Blashfield and McElroy noted (1), the scientific literature on personality disorders is rapidly growing. The development of a number of new instruments designed to assess personality disorder has paralleled and contributed to this growth. These include both structured interview schedules, such as the Personality Disorder Examination (2, 3), the Structured Clinical Interview for DSM-III-R Personality Disorders (SCID-II) (4), the Structured Interview for DSM-III Personality Disorders (5, 6), the Diagnostic Interview for Personality Disorders (7), and the Personality Interview Questions—II (8, 9), and self-report questionnaires, such as the Millon Clinical Multiaxial Inventory (10), the Personality Diagnostic Questionnaire—Revised (PDQ-R) (11), and the Wisconsin Personality Inventory (12).

Data are now being collected with all of these instruments, but little is known about the usefulness of one relative to another. For example, is a *DSM-III-R* axis II assessment according to an inexpensive self-report questionnaire essentially equivalent to a more time-consuming, costly clinician-conducted assessment, or is the extra effort and expense of the structured interview approach justified? The purpose of the study we describe was to assess the validity of the PDQ-R by comparing results obtained from the questionnaire to results obtained from two of the structured interviews, the Personality Disorder Examination and the SCID-II.

Previous studies of the Personality Diagnostic Questionnaire showed adequate test-retest reliability for many of the *DSM-III* personality disorders (13) and reported on the usefulness of the total score on this instrument as an indicator of overall personality disturbance (14). Results obtained in a comparison of PDQ diagnoses with specific personality disorder diagnoses reported by clinicians were less encouraging (15). The best agreement was on borderline personality disorder, for which the kappa coefficient of agreement was only 0.50. The use of routine clinical diagnoses of personality disorders as validity standards against which to compare the PDQ is limited, however, by the low reliability (16, 17) and questionable validity of clinical diagnoses. Structured interviews for axis II were developed to improve reliability and, therefore, were administered in this study to generate the diagnoses to be used as the validity standards.

The Personality Disorder Examination (May 15, 1985, version) and the SCID-II both yield *DSM-III-R* personality disorder diagnoses. They are differently constructed, however. In the Personality Disorder Examination, questions are grouped by various areas of functioning, e.g., work, self, interpersonal relationships, affect, reality testing, and impulse control. The number of questions pertaining to a given personality disorder criterion varies, and the number of positive responses necessary to meet a criterion is predetermined by a fixed algorithm. The person administering this version of the Personality Disorder Examination generally does not know which criteria are being met for a given *DSM-III-R* personality disorder. By contrast, in the SCID-II, questions are grouped according to sets of *DSM-III-R* criteria, and all questions pertaining to a single personality disorder are listed together. Most criteria are assessed by asking a single question; however, interviewers are encouraged to ask

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The authors thank Dr. Joseph Fleiss and Dr. Mark Davies for their advice on the statistical analyses.

additional questions to clarify ambiguous responses. The clinical judgment of the interviewer determines whether a particular criterion has been met. Using the SCID-II, the interviewer is well aware of whether the person being evaluated is meeting the criteria for each personality disorder.

There are advantages and disadvantages to each approach (18, 19). Thus, the problem of selecting an appropriate validity standard remains. Since neither of these structured interviews has been proven superior to the other, we thought it legitimate to compare diagnoses at two levels of certainty, defined by the convergence or divergence of results with the two contrasting structured interviews. When the two interviews agreed that a patient had a specific personality disorder, we assumed that this was a relatively "narrow" or conservative estimate of the presence of the disorder. In such cases, we believed that there was a strong likelihood that the patient actually had the disorder in question. When one of the interviews yielded a particular diagnosis but the other did not, we reasoned that this represented a "broader" estimate or definition of disorder, which indicated with less certainty that the disorder was present. We refer to the broad estimate as "probable" personality disorder and the narrow estimate as "definite" personality disorder. In evaluating the validity of the PDQ-R, we compared the diagnoses made according to that instrument with those of the Personality Disorder Examination and the SCID-II separately and in combination, using the definitions of probable and definite disorder.

## METHOD

The subjects for this study were 87 of 93 consecutive applicants for admission to the General Clinical Research Service of the New York State Psychiatric Institute between May 1986 and April 1988. The service provides long-term, psychodynamically oriented treatment to suitable inpatients with disabling character pathology. The subjects were predominantly women (74%, N=64), and their mean age was 27.6 years (range=17–44). Seventy-three (84%) were white, 71 (82%) had never married, and 70 (80%) had had at least some college education.

Before being evaluated for admission, all subjects were mailed the PDQ-R to complete and bring to their screening interview. It is a 152-item, self-administered true/false questionnaire that yields personality diagnoses consistent with the *DSM-III-R* criteria for all 11 axis II personality disorders and self-defeating personality disorder. It takes approximately 30 minutes to complete and can be scored by a nonprofessional.

On the day of clinical screening for admission, subjects were first evaluated for suitability for treatment on the service and then asked to participate in a study investigating methods of assessment. Informed consent was obtained after the procedures had been fully explained. Patients were then interviewed by two of three psychiatrists (S.E.H., A.E.S., H.D.K.) independently, one using the SCID (20) (axis I and axis II) and the other using the Personality Disorder Examination. The order of the two interviews was alternated, as was the psychiatrist administering them, in a balanced design. Both psychiatrists were blind to the results of the PDQ-R and of the clinical screening.

Since the purpose of this study was to investigate the relation of a self-report instrument for measuring personality disorders to structured instruments administered by psychiatrists, we deleted the self-report screen from the SCID-II; the psychiatrist inquired about all items.

At the time this study was being conducted, the criteria for personality disorders for *DSM-III-R* were being determined. As successive revisions of the criteria were published, we attempted to incorporate them simultaneously into the three instruments we used, so that the instruments given to any one subject were compatible, i.e., used the same set of criteria to define each disorder. A comparison of the initial draft (Oct. 5, 1985) of the *DSM-III-R* criteria for personality disorders with the final published version (May 1, 1987) reveals identical content in the criteria for a number of the disorders (e.g., schizotypal, histrionic, obsessive-compulsive, and passive-aggressive) and relatively minor differences in content for the others.

The validity of the PDQ-R was first assessed by comparing the prevalence of the individual personality disorders that it generated to the prevalence rates of the disorders according to the SCID-II and the Personality Disorder Examination. Next, we examined the chance-corrected agreement between the results of the PDQ-R, the SCID-II, and the Personality Disorder Examination. We also examined the concordance among the three instruments by using the intraclass correlation to assess rater reliability (21). Intraclass correlation and kappa are essentially equivalent for large-size samples such as ours. We assumed a two-way mixed model (instruments were considered fixed). Finally, using the definition of definite disorder (requiring agreement between Personality Disorder Examination and SCID-II diagnoses) or probable disorder (diagnosis generated by either instrument) as the criterion diagnosis, we assessed the sensitivity, specificity, and positive and negative predictive power of the specific personality disorder diagnoses according to the PDQ-R.

## RESULTS

The SCID assessment of current axis I disorders for these 87 patients showed that 57% (N=50) had mood disorders: 29% (N=25), major depression alone; 8% (N=7), major depression plus dysthymia; 5% (N=4), dysthymia alone; and 16% (N=14), bipolar disorder. In addition, 46% (N=40) had anxiety disorders, 20% (N=17) had psychoactive substance use disorders, 18% (N=16) met criteria for psychotic disorders (5% [N=4], schizophrenia), 21% (N=18) met criteria for

**TABLE 1. Prevalence of *DSM-III-R* Personality Disorders According to Three Diagnostic Instruments Among 87 Patients**

| Personality Disorder | PDQ-R | | SCID-II | | Personality Disorder Examination | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| Paranoid | 55 | 63 | 31 | 36 | 12 | 14 |
| Schizoid | 21 | 24 | 10 | 11 | 1 | 1 |
| Schizotypal | 28 | 32 | 18 | 21 | 18 | 21 |
| Antisocial | 12 | 14 | 5 | 6 | 7 | 8 |
| Borderline | 69 | 79 | 53 | 61 | 58 | 67 |
| Histrionic | 59 | 68 | 22 | 25 | 15 | 17 |
| Narcissistic | 30 | 34 | 15 | 17 | 19 | 22 |
| Avoidant | 51 | 59 | 47 | 54 | 36 | 41 |
| Dependent | 46 | 53 | 31 | 36 | 33 | 38 |
| Obsessive-compulsive | 47 | 54 | 17 | 20 | 21 | 24 |
| Passive-aggressive | 27 | 31 | 11 | 13 | 6 | 7 |
| Self-defeating | 38 | 44 | 34 | 39 | 20 | 23 |
| None | 7 | 8 | 10 | 11 | 20 | 23 |

eating disorders, and 5% (N=4) had somatoform disorders. Only 7% (N=6) of the sample had no axis I diagnosis.

Table 1 shows the prevalence rates of the *DSM-III-R* personality disorders as diagnosed by the three instruments. The PDQ-R diagnosed more patients as having each of the personality disorders than did either of the structured interviews. The SCID-II yielded more diagnoses, on average, than the Personality Disorder Examination. The finding of multiple personality disorder diagnoses was the rule for most of this sample, regardless of the instrument used. The mean±SD number of personality disorder diagnoses per patient for patients who had at least one of these diagnoses was 5.6±6.0 according to the PDQ-R, 3.4±3.8 according to the SCID-II, and 2.8±3.7 according to the Personality Disorder Examination.

Table 2 shows the chance-corrected agreement (kappa) between pairs of the three instruments and the intraclass correlation coefficients for the three simultaneously. Agreement between pairs of instruments was modest; the highest kappa was 0.70. The best agreement was generally between the two structured interviews. However, for several of the disorders and clusters, the PDQ-R agreed about as well with one or the other of the two interviews as they agreed with each other. Reliability among the three instruments was also modest.

Table 3 shows the kappa, sensitivity, specificity, and positive and negative predictive power of the PDQ-R diagnoses, with the definition of definite disorder (agreement between the Personality Disorder Examination and SCID-II diagnoses) or the definition of probable disorder (either Personality Disorder Examination or SCID-II diagnosis) as the criterion diagnosis. The sensitivities of the diagnoses generated by the PDQ-R were ≥0.80 for seven and nine of the 12 personality disorder diagnoses according to the definitions of probable and definite disorder, respectively. The specificities were generally in the 0.60–0.80 range. Similarly, the negative predictive powers were virtually all above 0.80; the positive predictive powers were considerably lower. Overall, the PDQ-R generated many false positive diagnoses but very few false negatives. The more stringent the definition of personality disorder used as the criterion, the more sensitive, but less specific, were the assessments according to the PDQ-R. The predictive value of a positive PDQ-R diagnosis increased as the criterion for a disorder was relaxed, but the predictive value of a negative PDQ-R evaluation decreased.

## DISCUSSION

Establishing the validity of any instrument for the diagnosis of personality disorders is difficult. In the absence of an infallible test or standard, choosing a criterion diagnosis is problematic. In this study, we used two psychiatrist-administered structured interviews, which approach the diagnostic process from different avenues, to give both broad and narrow definitions of personality disorders to be used as the criterion diagnoses. Other validity standards that tap central constructs of personality disorder, such as pervasiveness in many contexts and stability over time, are conceivable, but none is without problems. Diagnoses based on informed, multisource, longitudinal data have been proposed as validity standards for interview-based diagnoses (22) and have recently been used to validate SCID-II diagnoses (23). Other confirmatory strategies are needed for personality research.

Furthermore, the purpose of administering an instrument will influence an evaluation of its usefulness (24). Different properties of the instrument will be desirable depending, for example, on whether it is being used to evaluate patients for referral for possible treatment; to select patients for a particular comprehensive, expensive, or risky therapy; to identify confirmed cases for research studies; or to estimate the prevalence of a disorder in a nonpatient population.

In comparing the prevalence of PDQ-R diagnoses to that of SCID-II and Personality Disorder Examination diagnoses for our inpatient population, we found that the PDQ-R casts a broad net and overdiagnoses rather than underdiagnoses personality disorders. The weakest PDQ-R diagnoses appear to be schizoid and histrionic personality disorders, for which the PDQ-R yielded many more diagnoses than did the two structured interviews. For these disorders, the PDQ-R self-report gives an overabundance of false positive diagnoses that are judged by psychiatrists not to be clinically significant.

In comparing the PDQ-R with the two structured interviews, we found that levels of agreement were modest. For some diagnoses (e.g., schizoid, avoidant, and self-defeating) the PDQ-R showed better agreement with the SCID-II, and for some (e.g., narcissistic

**TABLE 2. Agreement Between the PDQ-R, the SCID-II, and the Personality Disorder Examination on *DSM-III-R* Personality Disorder Diagnoses for 87 Patients**

| Personality Disorder | Pairwise Kappa[a] | | | Three-Instrument Intraclass Correlation Coefficient |
|---|---|---|---|---|
| | PDQ-R Versus SCID-II | PDQ-R Versus Personality Disorder Examination | SCID-II Versus Personality Disorder Examination | |
| Cluster A | 0.34[b] | 0.29[b] | 0.28[c] | 0.36[b] |
| Paranoid | 0.27[d] | 0.12 | 0.27[d] | 0.30[b] |
| Schizoid | 0.43[b] | −0.02 | 0.16 | 0.24[d] |
| Schizotypal | 0.48[b] | 0.54[b] | 0.44[b] | 0.50[b] |
| Cluster B | 0.33[b] | 0.34[b] | 0.49[b] | 0.45[b] |
| Antisocial | 0.42[b] | 0.36[d] | 0.64[b] | 0.46[b] |
| Borderline | 0.53[b] | 0.46[b] | 0.53[b] | 0.53[b] |
| Histrionic | 0.24[d] | 0.18[c] | 0.56[b] | 0.40[b] |
| Narcissistic | 0.34[d] | 0.42[b] | 0.42[b] | 0.41[b] |
| Cluster C | 0.62[b] | 0.51[b] | 0.55[b] | 0.60[b] |
| Avoidant | 0.63[b] | 0.53[b] | 0.57[b] | 0.60[b] |
| Dependent | 0.57[b] | 0.52[b] | 0.70[b] | 0.62[b] |
| Obsessive-compulsive | 0.30[b] | 0.38[b] | 0.46[b] | 0.44[b] |
| Passive-aggressive | 0.23[c] | 0.21[c] | 0.29 | 0.27[b] |
| Self-defeating | 0.48[b] | 0.31[c] | 0.43[b] | 0.43[b] |

[a]The significance of each value of kappa was assessed by a chi-square test, with Yates' correction for continuity, of the hypothesis that agreement was greater than predicted by chance.
[b]$p<0.001$.
[c]$p<0.05$.
[d]$p<0.01$.

**TABLE 3. Kappa, Sensitivity, Specificity, and Positive and Negative Predictive Power of the PDQ-R for Definite and Probable Personality Disorder Diagnoses for 87 Patients**

| Personality Disorder | Definite Personality Disorder[a] | | | | | | Probable Personality Disorder[b] | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | Kappa[c] | Sensitivity | Specificity | Predictive Power: Positive | Predictive Power: Negative | N | Kappa[c] | Sensitivity | Specificity | Predictive Power: Positive | Predictive Power: Negative |
| Cluster A | 17 | 0.19[d] | 1.00 | 0.37 | 0.27 | 1.00 | 47 | 0.48[e] | 0.91 | 0.55 | 0.70 | 0.85 |
| Paranoid | 9 | 0.12 | 1.00 | 0.40 | 0.16 | 1.00 | 34 | 0.26[d] | 0.82 | 0.49 | 0.50 | 0.81 |
| Schizoid | 1 | −0.02 | 0.00 | 0.76 | 0.00 | 0.98 | 10 | 0.43[e] | 0.80 | 0.83 | 0.38 | 0.97 |
| Schizotypal | 10 | 0.43[e] | 1.00 | 0.77 | 0.36 | 1.00 | 26 | 0.57[e] | 0.73 | 0.85 | 0.68 | 0.88 |
| Cluster B | 50 | 0.27[e] | 1.00 | 0.24 | 0.64 | 1.00 | 69 | 0.44[e] | 0.97 | 0.39 | 0.86 | 0.78 |
| Antisocial | 4 | 0.33[e] | 0.75 | 0.89 | 0.25 | 0.98 | 8 | 0.44[e] | 0.62 | 0.91 | 0.41 | 0.96 |
| Borderline | 46 | 0.41[e] | 0.98 | 0.41 | 0.65 | 0.94 | 65 | 0.68[e] | 0.95 | 0.68 | 0.90 | 0.83 |
| Histrionic | 12 | 0.14[f] | 1.00 | 0.37 | 0.20 | 1.00 | 25 | 0.28[e] | 0.96 | 0.43 | 0.35 | 0.96 |
| Narcissistic | 9 | 0.30[e] | 0.89 | 0.71 | 0.27 | 0.98 | 25 | 0.44[e] | 0.68 | 0.79 | 0.57 | 0.86 |
| Cluster C | 47 | 0.52[e] | 1.00 | 0.50 | 0.70 | 1.00 | 65 | 0.62[e] | 0.92 | 0.68 | 0.90 | 0.75 |
| Avoidant | 32 | 0.49[e] | 0.93 | 0.60 | 0.59 | 0.94 | 51 | 0.67[e] | 0.86 | 0.80 | 0.86 | 0.80 |
| Dependent | 26 | 0.51[e] | 0.96 | 0.66 | 0.54 | 0.98 | 38 | 0.59[e] | 0.87 | 0.73 | 0.67 | 0.88 |
| Obsessive-compulsive | 11 | 0.22[d] | 1.00 | 0.53 | 0.23 | 1.00 | 27 | 0.47[e] | 0.93 | 0.63 | 0.53 | 0.95 |
| Passive-aggressive | 3 | 0.15[f] | 1.00 | 0.71 | 0.11 | 1.00 | 13 | 0.25[f] | 0.61 | 0.74 | 0.30 | 0.92 |
| Self-defeating | 16 | 0.25[f] | 0.75 | 0.63 | 0.31 | 0.92 | 38 | 0.53[e] | 0.74 | 0.80 | 0.74 | 0.80 |

[a]Diagnosed according to both the SCID-II and the Personality Disorder Examination.
[b]Diagnosed according to either the SCID-II or the Personality Disorder Examination.
[c]The significance of each value of kappa was assessed by a chi-square test, with Yates' correction for continuity, of the hypothesis that agreement was greater than predicted by chance.
[d]$p<0.01$.
[e]$p<0.001$.
[f]$p<0.05$.

and schizotypal) it showed better agreement with the Personality Disorder Examination. Agreement between the SCID-II and the Personality Disorder Examination was also modest, however, and for about half of the personality disorders the PDQ-R agreed with either of the two interviews about as well as they agreed with each other. The reasons for the disagreements between the structured interviews will be the focus of another report (Skodol et al., unpublished manuscript). In interpreting the levels of agreement shown in the results, instances in which the agreement of the PDQ-R with one of the structured interviews

approaches (or exceeds) the level of agreement between the SCID-II and the Personality Disorder Examination may be the best that can be expected.

These results show that the PDQ-R is not a substitute for a structured interview. It is also evident, however, that one structured interview is not necessarily a substitute for another; they may yield different results. Thus, we urge investigators to use caution in comparing their findings with those of others when different instruments have been used for personality disorder diagnosis.

In examining the sensitivity, specificity, and positive and negative predictive power of the PDQ-R diagnoses for our two definitions of personality disorder, we found that the PDQ-R showed excellent sensitivities; the specificities ranged from poor for histrionic personality disorder to excellent for antisocial personality disorder. The relatively high values for negative predictive power indicate that when the PDQ-R fails to make a diagnosis (by either criterion), the disorder is most likely absent. However, if the PDQ-R makes a diagnosis of a specific personality disorder (positive predictive power), it may be a false positive.

Our results indicate that the PDQ-R may be useful in screening for personality disorders in psychiatric patients, at least when personality disorders are expected to be common. The patients in this study were drawn from a population in which a high degree of personality pathology was expected. In fact, according to either structured interview, the prevalence was >0.30 for at least one-fourth of the disorders, >0.20 for at least half, and >0.10 for at least three-fourths. Summing across all three instruments, these patients averaged almost four personality disorders each. The positive predictive power of a PDQ-R diagnosis will be less in populations with smaller personality disorder base rates if the same cutoff points are used. The relative risk of actually having a disorder diagnosed by the PDQ-R, however, may remain the same or even increase. We are currently studying the screening properties of the PDQ-R with patients applying for psychoanalysis, who, we anticipate, will have substantially less personality psychopathology. Currently, the PDQ-R is scored by using fixed cutoff points established by *DSM-III-R* criteria. A flexible cutoff point system may be needed to maximize the usefulness of the instrument in screening diverse populations and for different clinical and research purposes.

The agreement between the PDQ-R, the SCID-II, and the Personality Disorder Examination assessed simultaneously can also be interpreted as a measure of concurrent or convergent validity of the personality disorder constructs themselves. From this perspective, none of the disorders stands out, although dependent and avoidant personality disorders show some consistency in measurement, and schizoid and passive-aggressive personality disorder appear particularly weak.

The clinical importance of personality disorders is becoming increasingly apparent. Axis II psychopathology has been shown to adversely affect treatment response in major depression (25, 26) and panic disorder (27). Furthermore, personality disorders may have accounted for a considerable portion of the population in the Epidemiologic Catchment Area study who sought mental health services but had no disorder according to the Diagnostic Interview Schedule (28). Therefore, recognition of personality disorders in clinical and research settings should receive greater emphasis.

We believe that the PDQ-R may be used to screen individuals to be studied further for specific personality disorders. We recommend that positive diagnoses according to the PDQ-R be verified for clinical significance by clinician-administered interviews. This two-step process could result in significant savings in clinicians' time in comparison to a complete evaluation of all patients for each of the personality disorder diagnoses. For certain disorders, such as avoidant and dependent, the PDQ-R self-report diagnoses may need less verification than for others, such as paranoid and histrionic. Our results lend empirical support for the recommended format of the SCID-II, that is, a self-report questionnaire followed by structured interview assessment primarily of items marked "true."

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# Psychiatric Symptoms and Nursing Home Placement of Patients With Alzheimer's Disease

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*Two hundred ten community-dwelling patients with Alzheimer's disease were examined prospectively by psychiatrists as part of a longitudinal study. Twenty-five of these patients who were institutionalized during the next 3 years were then matched to 25 patients who were not institutionalized, and the groups were compared. The patients who had been institutionalized had higher scores on standardized psychiatric rating scales but not on formal neuropsychological tests of cognition. These results suggest that potentially treatable (noncognitive) behavioral and psychiatric symptoms are risk factors for institutionalization, and that treating these symptoms might delay or prevent institutionalization of some patients.*

(Am J Psychiatry 1990; 147:1049–1051)

A large proportion of the 1.5 million patients in nursing homes are demented, and the most common cause is Alzheimer's disease (1, 2). Because the cognitive symptoms are presently untreatable, identifying potentially treatable symptoms such as depression, delusions, and hallucinations is especially important (3, 4). These symptoms are particularly prevalent in nursing home populations, but few studies have determined to what extent they are the cause or the consequence of institutionalization. Previous studies have indicated that incontinence, aphasia, dependency in activities of daily living, severity of cognitive impairment, and sleeplessness predict institutionalization (5, 6). Behavioral and mood disturbances also emerge as predictors, but no studies have included a systematic longitudinal psychiatric assessment of patients before they are admitted to nursing homes (7, 8). If these behavioral symptoms occur before institutionalization and are risk factors for placement in an institution, then treating them may delay or avoid placement of the patient in a nursing home. This could have important public health consequences, since it might reduce the estimated $23 billion annual cost of nursing home care for demented patients. In this preliminary study, we investigated whether potentially treatable symptoms such as depression and behavioral disturbances in Alzheimer's disease patients would predict nursing home admission.

## METHOD

A series of 210 noninstitutionalized patients with possible or probable Alzheimer's disease according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association were recruited for the Johns Hopkins University Alzheimer's Disease Research Center longitudinal study in 1984 (9). The patients were drawn from multiple sources, including outpatient psychiatry and neurology clinics at Johns Hopkins and the community at large. The methods of assessing the patients have been described elsewhere (10); they included review of medical records and laboratory tests, neuropsychological testing, neurological, physical, and psychiatric examinations, and interviews with informants to establish evidence of functional decline. A psychiatrist examined each patient with a modified version of the Present State Examination (11) to elicit psychiatric symptoms and completed the Brief Psychiatric Rating Scale (BPRS) (12) and the Hamilton Rating Scale for Depression (13) after each examination. Interrater reliability was established on all instruments.

After entry into the study, the subjects were examined and their caregivers interviewed at 6-month intervals. The battery of neuropsychological tests administered at each visit included the Mini-Mental State examination (14), a 30-item short form of the Boston Naming Test (15) (visual confrontation naming), the Category Fluency Test (16) (word list generation), and

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Supported by grant AG-05146 from the National Institute on Aging.

The authors thank Laura Filipp, M.H.S., for assistance in carrying out this study.

**TABLE 1. Scores on Cognitive, Behavioral, and Psychiatric Measures of 25 Pairs of Institutionalized and Noninstitutionalized Patients With Possible or Probable Alzheimer's Disease**

| Measure | Institutionalized Patients | | Noninstitutionalized Patients | | Wilcoxon Matched-Pairs Signed Ranks Test (two-tailed) | |
|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | T (N=25) | p |
| Cognitive | | | | | | |
| Mini-Mental State | 9.6 | 5.8 | 12.1 | 6.7 | 107 | 0.22 |
| Boston Naming Test | 9.0 | 8.7 | 11.4 | 8.5 | 109 | 0.34 |
| Category retrieval | 10.4 | 10.7 | 13.2 | 12.4 | 120 | 0.39 |
| Recognition span | 2.8 | 2.6 | 3.6 | 2.1 | 111 | 0.27 |
| Psychogeriatric Dependency Rating Scales | | | | | | |
| Orientation | 3.6 | 2.4 | 2.3 | 2.1 | 64 | 0.04 |
| Behavior | 7.6 | 5.8 | 4.0 | 4.1 | 53 | 0.02 |
| Physical functioning | 11.5 | 6.4 | 6.8 | 7.5 | 43 | 0.002 |
| Psychiatric | | | | | | |
| Hamilton depression scale | 7.9 | 4.7 | 3.0 | 3.3 | 33 | 0.002 |
| BPRS | 1.9 | 0.5 | 1.6 | 0.3 | 50 | 0.02 |

the Spatial Delayed Recognition Span Test (17) (nonverbal recognition memory). The Psychogeriatric Dependency Rating Scales (18) were completed at each visit to assess function in three areas: orientation to self, caregivers, and surroundings; frequency of problematic behavior; and physical functioning in activities of daily living. This instrument is a standardized observer rating scale for use with elderly institutionalized patients. Higher scores indicate greater impairment. The behavior subscale includes commonly occurring behavior such as physical aggressiveness, wandering, disruptiveness, and restlessness.

By June 1987, 25 (12%) of the sample had been admitted to nursing homes. We used a matched-pair design to examine the patient characteristics that were associated with institutionalization. Each of the 25 institutionalized patients was matched to a noninstitutionalized patient of the same sex, race, age, education, and marital status. We compared data from the institutionalized subjects' last visit to the center before placement in a home and data from the most recent visit of the noninstitutionalized subjects. The following variables were studied: duration of illness, scores on cognitive measures, psychiatric symptoms, frequency of problematic behavior, and dependency in activities of daily living. The ratings on these variables for the institutionalized subjects and the noninstitutionalized comparison subjects were evaluated by means of the Wilcoxon matched-pairs signed ranks test.

Complete matching of the 25 pairs of subjects was achieved for race (84% white and 16% black), sex (24% male and 76% female), and marital status (44% married and 56% single). Distributions were comparable for the institutionalized and comparison subjects on age (mean±SD=70.7±6.7 and 71.2±6.6 years, respectively; t=−1.26, df=24, p=0.22) and education (12.7±3.6 and 12.2±2.9 years, respectively; t=1.21, df=24, p=0.24).

## RESULTS

There was no significant difference between the two groups in mean±SD duration of illness (institutionalized, 5.04±2.64 years; comparison group, 4.52±1.98 years; T=55, N=25, p=0.50). Table 1 shows the cognitive, behavioral, functional, and psychiatric characteristics of the institutionalized and matched noninstitutionalized patients. The institutionalized patients had higher scores on the Hamilton depression scale, the BPRS, and the behavior disorder subscale of the Psychogeriatric Dependency Rating Scales on their last visit to the center before being placed in a nursing home. The higher scores on the behavior disorder subscale indicate more frequent behavior problems such as wandering, combativeness, and resisting caretaking efforts. The BPRS abnormalities included higher degrees of suspiciousness and hallucinatory behavior.

The institutionalized patients also scored higher on the activities of daily living and orientation subscales of the Psychogeriatric Dependency Rating Scales, indicating greater impairment in capacity for self-care and orientation to caregiver and environment. However, there was no significant difference on any of the formal cognitive measures.

## DISCUSSION

The sample we studied was small but carefully diagnosed and thoroughly assessed. Unlike previous studies, we used psychiatric as well as cognitive rating scales with known reliability and validity, thereby increasing our confidence in the accuracy of the findings. The findings advance previous observations that behavioral problems are associated with institutionalization, since we studied these problems prospectively and used standardized methods to assess and quantify them. We found that potentially reversible psychiatric

symptoms such as depression and agitation were among the important predictors of nursing home placement. This suggests that psychiatric intervention and treatment might prevent or delay institutionalization.

Psychiatric symptoms were not the only predictors of admission, since the institutionalized patients were also more disabled in activities of daily living. This confirms Hutton et al.'s report (5) that impairment in physical functioning is an important predictor of nursing home placement. Our data indicate that the combination of behavior disorder and functional impairment predicts placement. While the design of this study did not allow us to determine the effects of behavior disorder on functional impairment, we have previously shown (9) that depression in Alzheimer's disease is associated with greater functional disability.

We found no differences between the institutionalized and noninstitutionalized patients on standard cognitive tests such as the Mini-Mental State, the Boston Naming Test, the Spatial Delayed Recognition Span Test, and the Category Fluency Test, suggesting that severity of cognitive impairment is not a major risk factor for institutional placement. This disagrees with reports by Heyman et al. (6) and Knopman et al. (7). Heyman et al. indicated that lower scores on the Mini-Mental State, the WAIS, and the Aphasia Screening Test were associated with increased risk of institutionalization, and Knopman et al. found similar results using Blessed's Information, Concentration, Memory Test. However, Heyman et al. studied a sample of patients with early Alzheimer's disease, which is associated with rapid deterioration of cognitive function. Knopman et al. examined subjects at their initial visit and then followed them through caregiver interviews for the next 2–4 years. Thus, their cognitive data were collected between 2 and 4 years before patients were institutionalized. They also found that behavioral disturbances were associated with institutionalization. Our results are consistent with other studies showing that on admission to nursing homes, many demented patients suffer from noncognitive psychiatric symptoms, and family members often cite behavior disorders as primary reasons for admission (7, 19). Multiple factors, such as the health of the caregiver and the composition of the family, undoubtedly contribute to the decision to place a relative in a nursing home. Future studies might assess the relative contributions of these factors and their interaction with patients' behavior disorders.

These results must be interpreted cautiously because of the limitations in the method. Matched-pair design controls variables such as sex, education, and marital status, and thus the impact of these variables on outcome could not be examined. Also, the sample size did not allow for analysis of the interactions among variables or examination of psychiatric and behavioral symptoms alone. We are now conducting an incidence case-control study to explore these additional variables. Despite the limitations, this preliminary study indicates the need for prospective studies to test the hypothesis that treatment of noncognitive psychiatric and behavioral symptoms, such as depression, delusions, hallucinations, and aggressiveness, in patients with Alzheimer's disease can prevent or delay nursing home placement.

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# Prediction of Adult-Onset Schizophrenia From Childhood Home Movies of the Patients

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*In a preliminary study of developmental precursors of schizophrenia, home movies of adult-onset schizophrenic patients and their healthy siblings filmed during their childhood were viewed by judges who were blind to the psychiatric outcome of the subjects. The films began with the infancy of all subjects and extended through at least the first 5 years of their lives. Although none of the subjects had any psychiatric disorder in childhood, the preschizophrenic children were reliably identified by the viewers. This represents the first demonstration that preschizophrenic subjects can be distinguished from sibling control subjects within the first 8 years of life by observing their behavior.*

(Am J Psychiatry 1990; 147:1052–1056)

Schizophrenia has generally been conceptualized as an adult-onset disorder, because the modal age at clinical onset is 20–25 years (1). However, there is reason to believe that the neuropathology underlying schizophrenia may be present early in life, perhaps at birth (2–5). The results of twin and adoption studies, as well as recent genetic linkage studies, indicate that heredity plays a role in schizophrenia (1). Obviously, in cases where genetic factors are operative, constitutional vulnerability would be congenital. Further support for congenital vulnerability comes from findings that a subgroup of schizophrenic patients manifested brain abnormalities on CT and magnetic resonance imaging scans that suggested long-standing structural impairment (4). However, despite the widespread assumption that at least some schizophrenic disorders involve a neuropathology that is present at birth, we have little knowledge of the developmental course that precedes the clinical onset of the disorder. Lewis (6) has pointed out that "the enormous efforts that have been made in defining a phenotype in cross-section have not yet been matched by proper consideration of longitudinal features."

To date, information on the developmental precursors of adult-onset schizophrenia has come from three sources: retrospective reports, follow-back studies, and prospective research on high-risk subjects. Investigations based on retrospective parental reports have yielded inconsistent results; for example, some suggest that there is a higher incidence of perinatal and early infancy complications among preschizophrenic individuals, and others do not (7, 8). The potential unreliability of retrospective data provided the impetus for follow-back studies of school records (grades, test scores, and teachers' anecdotal comments about the child's behavior). With the use of this latter method, the earliest point at which preschizophrenic subjects were distinguishable from control subjects on the basis of classroom behavior was early adolescence; the preschizophrenic subjects showed greater behavioral problems (9). Significant deficits in test scores have been found in schizophrenic patients as early as the first grade (10).

Prospective studies of the developmental precursors of schizophrenia in high-risk subjects have focused on the biological offspring of schizophrenic parents (11). The subjects of most of these studies have not passed through the major risk period for schizophrenia, so the outcomes are not yet known. However, offspring of schizophrenic parents have been shown to manifest deficits in motor, cognitive, and interpersonal functioning when compared to children of normal parents (11). The question of whether these deficits are uniquely related to schizophrenic disorders in adulthood remains unanswered (12).

The fact that we know so little about the developmental precursors of schizophrenia has been a major obstacle in our efforts to generate etiological models of the disorder. Specifically, the following critical questions must be addressed. 1) Are individuals who develop schizophrenia in adulthood distinguishable from control subjects in childhood? 2) What is the earliest point in the life course that signs of vulnerability are apparent? 3) What is the nature of the manifestations of vulnerability?

The present investigation represents a first step in our attempt to address these questions through the application of an "archival-observational" approach that uses home movies of patients when they were children as the primary database on development. The use of home movies provides a unique opportunity for di-

Received July 28, 1989; revision received Nov. 14, 1989; accepted Jan. 25, 1990. From the Department of Psychology, Emory University. Address reprint requests to Dr. Walker, Department of Psychology, Emory University, Atlanta, GA 30322.

rectly examining the childhood behavior of individuals whose adult psychiatric outcome is known. Moreover, healthy siblings serve as an ideal comparison group because they are featured in the same films within the same behavioral contexts. In future research we will use systematic observational procedures to obtain data on the socioemotional and neuromotor development of the subjects. The central goal in this preliminary study was to determine whether viewers who were blind to the adult psychiatric outcome of the subjects would be able to distinguish the preschizophrenic children from their healthy siblings. Specifically, we sought to determine whether the preschizophrenic children could be reliably identified before they were 8 years of age. We expected the findings from this preliminary study to shed light on the feasibility of this new method for exploring developmental precursors. Further, before subjecting the films to analysis with microlevel coding schemes, it was important for us to know whether the viewers would be capable of detecting the target children without the benefit of specific criteria.

## METHOD

Although the patients and their siblings are the focus of this research program, the individuals viewing the films were the actual subjects of the present study. The viewers were graduate students in psychology (N=13) and experienced clinicians (N=6). The experienced clinicians were four doctoral-level psychologists, one psychiatrist, and one master's-level psychiatric nurse. With the exception of one psychologist who is now primarily involved in developmental research, all of the experienced viewers were actively engaged in work with psychiatric patients at the time of the study (one with adults only and the others with both children and adults).

The subjects featured in the films are five schizophrenic patients (four male and one female) and their healthy siblings who are past the age of 25 years and have no history of psychiatric disorder. Subjects were selected from a larger sample of 15 patients on the basis of criteria that we shall describe. Informed consent was obtained from the participants after the procedures and goals of the study had been fully explained.

In every case, the patient was the only one in his or her nuclear family who had a psychiatric disorder. The patients were diagnosed as schizophrenic in late adolescence or early adulthood and have been under continuous medical care since the onset of their illness (current mean±SD age of the patients=29±5.2 years). None of the patients was referred for or received treatment for psychiatric problems before the age of 17, nor did any of them have physical illnesses or handicaps that would set them apart from their siblings. All of the patients currently meet the *DSM-III-R* criteria for schizophrenia. Diagnostic information was gathered through a structured clinical interview, the Schedule for Affective Disorders and Schizophrenia (SADS) (13), with the subject and medical history information provided by the parents. The diagnostic interviewer was a doctoral-level psychologist (E.W.) trained in the administration of the SADS. Three of the five patients were also independently given diagnoses by another interviewer using the SADS, and there was 100% consensus.

All available 8- and 16-mm home movies of the patients and their siblings were submitted for study. These were transcribed to videotape, and the tapes were edited to eliminate footage that did not feature one or more of the children in the sibship. The ages of the children in the films were determined on the basis of information provided by the parents as well as the film content. Chronologically ordered segments were prepared for viewing. Because the children enter the films in order of birth, some of the initial segments did not include all of the children in a sibship. However, all segments included all children born before the date on which the segment ended. Also, because the siblings enter the films in order of birth and are subsequently featured simultaneously in the films, it was not possible to make the length of time they were featured or the age span covered the same for all children within a sibship. However, for all subjects, the films included footage taken during the first 17 months of life and extended to at least the fifth year.

The viewers were blind to the identity and psychiatric status of the subjects in the films. They were informed that they would be viewing videotape segments of sibships in which only one child developed schizophrenia later in life. To avoid biasing the viewers by directing their attention to particular characteristics of the subjects, we provided no criteria for judging the children. The viewers were instructed to use their own criteria in judging the eventual psychiatric status of the children and to note on their response forms the factors that influenced their judgments. In this way we could determine which features of the children were most salient to the individual viewers in making their judgments. We provided the viewers with standard forms on which to record their responses and instructed them to remain silent while viewing the videotapes and refrain from sharing their responses with others.

The viewers were informed of the ages of the children featured in each of the chronologically ordered segments. After each segment was shown, they were asked to respond yes or no (forced choice) to the question "Is this the preschizophrenic child?" They were to choose one and only one child from the sibship. Once they recorded their judgments, the viewers were not permitted to change them; however, they were free to judge the children differently after viewing subsequent segments. In cases where the initial film segment included only a subset of the siblings, viewers were not required to choose one of them. In addition to the forced-choice response, the viewers were asked to in-

dicate their confidence in their judgment of each child on a 4-point scale: 0=no confidence, 1=somewhat confident, 2=confident, 3=very confident.

We used a forced-choice procedure so that the resultant data would be suitable for probability analyses. Further, with this procedure individual differences among viewers in decision or response thresholds (i.e., threshold for affirmative responses) do not influence outcomes.

A pilot study was conducted with films of one male patient and his siblings to determine the suitability of the rating procedures. A group of seven graduate students in psychology viewed 10 film segments (5–10 minutes each) of the sibship, which was composed of five children (four male and one female); the patient was the second born. He had shown an onset of symptoms at 22 years of age, at which time he first received treatment. The total duration of the videotape was 60 minutes, and it began with the birth of the first child and extended to the fifth birthday of the last-born child. We subjected the final judgments of the viewers (i.e., those made after viewing all segments of the film) to the binomial test, using the tables listing the critical values for binomial judgments, with varying probabilities of events, in the textbook by Runyon and Haber (14). In their final judgments, five of the seven viewers correctly identified the preschizophrenic child, although there was no relation between confidence ratings and accuracy. The probability (p) value associated with five of seven correct, when P=0.20 and Q=0.80, is <0.05. Moreover, the p value associated with the proportion of correct judgments was <0.05 by the time the preschizophrenic child was 5 years of age. This result is striking in light of the parents' report that they had detected no signs of impending disorder in the child until he reached adulthood and that, in fact, he was the child that they would have least expected to develop an adjustment problem. The viewers' written comments indicated that some of them perceived the preschizophrenic child as manifesting atypical emotional expressions and movements.

The results of the pilot study confirmed the appropriateness of the rating scheme. However, to reduce the time required for collecting ratings on a sibship, procedures for subsequent data collection were modified so that a maximum of four segments per sibship were viewed. Selection of subjects for this study was based on three additional criteria: 1) that home movies of the patient and siblings span at least the first 5 years of life, 2) that the maximum age difference among the siblings within each sibship not exceed 6 years, to facilitate comparison, and 3) that the total duration of the movies of each sibship be at least 40 minutes. Four sibships from a total sample of 15 sibships on whom films were submitted met these criteria.

The mean age at first diagnosis for the patients in the four sibships was 20.5 years (range=17–24 years). Because of variations in the amount of film on each sibship, the number of segments (15–20 minutes each) per sibship varied, with two segments for one and four segments for three. For sibships 1–3, the videotapes exceeded 80 minutes, so segments were selected in such a way that each sibling would be shown between birth and 17 months and at least up to 5 years of age. Using the criterion of featuring each child up to age 5 resulted in the preschizophrenic subjects being featured to a maximum mean±SD age of 6.25±0.69 years and the sibling controls to 7±6 years. There was no significant difference between the patients and the control siblings in mean duration of time featured. For this study, the viewers were graduate students in psychology (N=6) and experienced clinicians (N=6). (The six graduate students and one experienced clinician viewed all the sibships, and the other viewers judged only the first two or three sibships.) Videotapes were shown to the group of viewers on a 25 × 25 inch monitor in a classroom.

## RESULTS

Table 1 lists the characteristics of the sibships, the number of viewers rating the sibships, and the viewers' judgments of the children after each segment.

The binomial test was used to determine the probabilities associated with the numbers of correct judgments in response to the segments that included all members of the sibship. The significant ($p<0.05$, one-tailed tests) and marginally significant ($p<0.10$) p values associated with these judgments for each sibship are shown in table 1. In two cases the p values were equal to 0.10 at the final judgment, and in two cases they were <0.05. For sibship 1, the p value was <0.05 following the third viewing segment—the point at which the preschizophrenic child was less than 1 year of age. When the results from the three sibships containing two children are combined, the total number of correct judgments is 25 of 32 ($p<0.05$). (Data from the sibship of three could not be included in the combined analysis because the chance probability for correct judgment is 0.33 rather than 0.50.)

There was no significant relation between the accuracy of judgments and the confidence ratings or clinical experience of the viewers. As in the pilot study, some viewers commented on interpersonal and/or motor characteristics of the children. Recorded observations about the preschizophrenic children noted less responsiveness, eye contact, and positive affect and poorer fine and gross motor coordination. It is interesting that when viewers failed to detect the preschizophrenic child, they made fewer comments on the characteristics of the child. However, when comments were made, they also concerned motoric and affective characteristics.

## DISCUSSION

This investigation is the first to provide evidence that through observation of their behavior, individuals

**TABLE 1. Viewers' Judgments About Which Child Was Preschizophrenic After Watching Segments of Home Movies of Children in Four Sibships**

| Sibship Number/ Sex of Child | First Segment | | Second Segment | | Third Segment | | Fourth Segment | |
|---|---|---|---|---|---|---|---|---|
| | Age Span of Child | Viewers Who Said Child Was Preschizophrenic | Age Span of Child | Viewers Who Said Child Was Preschizophrenic | Age Span of Child | Viewers Who Said Child Was Preschizophrenic | Age Span of Child | Viewers Who Said Child Was Preschizophrenic |
| 1 (12 viewers) | | | | | | | | |
| Child 1: F | 5–11 mo | 7 | 5–5½ years | 5 | 5½–6 years | 2 | 9–10 years | 2 |
| Child 2: M[a] | (Not born) | — | 1–4½ mo | 7 | 4½–11 mo | 10[b] | 4–5 years | 10[b] |
| 2 (12 viewers) | | | | | | | | |
| Child 1: F[a] | 10 mo–1 year | 5 | 1–2 years | 6 | 2–3 years | 6 | 4–7 years | 9[c] |
| Child 2: F | (Not born) | — | 1–4 mo | 6 | 4–14 mo | 6 | 3–5 years | 3 |
| 3 (eight viewers) | | | | | | | | |
| Child 1: M[a] | 1–6 mo | 7 | 1–2 years | 6[c] | 3–4 years | 5 | 4–6 years | 6[c] |
| Child 2: M | (Not born) | — | 1–10 mo | 2 | 1–2 years | 3 | 2–5 years | 2 |
| 4 (seven viewers) | | | | | | | | |
| Child 1: F | 1–4 years | 5 | 6–10 years | 0 | | | | |
| Child 2: M[a] | 3 mo–1 year | 2 | 3–7 years | 5[b] | | | | |
| Child 3: F | (Not born) | — | 1–5 years | 2 | | | | |

[a]The preschizophrenic child.
[b]$p<0.05$.
[c]$p=0.10$.

who become schizophrenic patients in early adulthood can be differentiated from their healthy siblings before the age of 8 years. These findings are noteworthy for several reasons. First, they lend support to the notion that the diathesis presumed to underlie schizophrenia is present long before the onset of psychotic symptoms. Second, the fact that the viewers identified the preschizophrenic children at above-chance levels without being instructed to use specific criteria suggests that the distinguishing characteristics of these children are apparent at a gross level of analysis. Third, the results indicate that the archival-observational approach to the study of developmental precursors holds promise for illuminating the pathways leading to schizophrenia.

The present findings should not be taken to imply that all individuals who eventually develop schizophrenia can be distinguished from their siblings in childhood. It should also be noted that the characteristics of the preschizophrenic children that determined the viewers' judgments may not be direct manifestations of the schizophrenic diathesis but, rather, nonspecific signs of vulnerability that are associated with increased risk for a variety of disorders. We will attempt to address this issue in future studies that will compare various diagnostic groups. With respect to the method used here, two limitations should be noted. Because access to cameras for making home movies is likely to be associated with higher socioeconomic status, the subjects in this research tended to be from middle- and upper middle-class families. Also, the films present only a small sample of behavior. On the other hand, the fact that the viewers detected the preschizophrenic children despite the relatively brief samples of behavior suggests that the effect is robust.

As previously mentioned, subsequent analyses of films will involve microlevel coding of the neuromotor and socioemotional characteristics of the children. This will enable us to specify more precisely the nature of the differences between the preschizophrenic and the control subjects. In addition to comparison with siblings, schizophrenic patients will be compared with a psychiatric group (patients with affective disorders) and normal control subjects from families with no mental illness in first-degree relatives. Emphasis will be placed on identifying neuromotor signs that may shed light on underlying neuropathology.

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# Failure to Detect Fabricated Posttraumatic Stress Disorder With the Use of the MMPI in a Clinical Population

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*The authors attempted to replicate previous studies that used the Frequency (F) scale and the posttraumatic stress disorder (PTSD) subscale of the MMPI to discriminate Vietnam veterans with PTSD from well-adjusted veterans and mental health professionals who feigned symptoms of PTSD. Profiles of veterans with PTSD were compared to those of veterans with non-PTSD psychiatric disorders and veterans with fabricated PTSD symptoms who sought treatment. Discriminant analysis of F scale and PTSD subscale scores correctly identified only 43.59% of the subjects, thus failing to support use of the MMPI in detecting fabricated symptoms of PTSD in a clinical population.*

(Am J Psychiatry 1990; 147:1057–1060)

Several studies (1–3) have examined the use of the MMPI as an aid to diagnosing posttraumatic stress disorder (PTSD) in Vietnam combat veterans. Generally, these studies have demonstrated successful use of the MMPI to differentiate veterans with combat-related PTSD from well-adjusted veterans. More recently, investigators have attempted to use this instrument to detect fabricated symptoms of PTSD and have reported an impressive degree of success (4, 5).

In one study Fairbank et al. (4) instructed well-adjusted veterans and mental health professionals familiar with the symptoms of PTSD to respond to questions on the MMPI as they thought patients with the disorder would respond. The MMPI Frequency (F) scale and the 49-item MMPI PTSD subscale (2) were used in an effort to discriminate between these subjects and Vietnam veterans who actually had diagnoses of PTSD. A discriminant analysis of the predictor variables correctly classified 93% of the subjects in the sample; none of the veterans with "factitious disorder" and only one of the mental health professionals with factitious disorder was misclassified.

These findings were replicated in a study by McCaffrey and Bellamy-Campbell (5) that had one modification. In their study, Vietnam veterans who were mental health professionals were used along with well-adjusted veterans to provide the factitious responses on the MMPI. The MMPI F scale and PTSD subscale correctly classified 91.4% of the total sample, and none of the veterans from the two groups with "factitious PTSD" was misclassified as actually having PTSD. The decision rule devised by Fairbank et al. (4) correctly classified 89% of the total sample in this study.

While the initial results of these two studies were quite impressive, two concerns must be addressed. First, several studies (6–9) have investigated the overreporting of symptoms on the MMPI by veterans with PTSD who served in Vietnam. Hyer et al. (7) suggested that overreporting of symptoms is often a part of the PTSD clinical presentation in Vietnam veterans, and they advised caution in using the PTSD subscale of the MMPI. In a subsequent study (9), it was found that all of the Vietnam war veterans who were assessed (especially those who had served in that country) overreported symptoms to a high degree and that the veterans scoring in the high range on the PTSD subscale also generally had high MMPI F-K index scores. The results of these studies clearly call into question any use of the MMPI to differentiate between PTSD and factitious disorders on the basis of elevated F scores and PTSD subscale scores.

Perhaps of even greater concern in the two fabricated-symptom studies is the generalization of the results from well-adjusted veterans and mental health professionals attempting to fabricate symptoms of PTSD to veterans with actual factitious disorders. First, it is unclear to what population the generalization is meant to extend when these investigators refer to "factitious PTSD." Since veterans with no service in Vietnam who present with PTSD symptoms are relatively easy to detect by checking their discharge papers, it is more important that psychometric decision rules assist in detecting veterans who did serve in Vietnam and are fabricating or exaggerating symptoms of PTSD. However, it is likely that this is a rather heterogeneous population, as there are any number of reasons to fabricate symptoms of a psychiatric disorder, one of which is the presence of a factitious disorder. Veterans may also fabricate symptoms for purposes of compensation or to escape consequences of antisocial or criminal behavior (i.e., malingering). There have been several documented cases of the use of a PTSD diagnosis as a de-

Received Aug. 18, 1989; revision received Dec. 11, 1989; accepted Jan. 25, 1990. From the Highland Drive VA Medical Center. Address reprint requests to Dr. Perconte, Psychology Service (116B), Highland Drive VA Medical Center, Pittsburgh, PA 15206.

fense in criminal trials (10). Using mental health professionals and well-adjusted veterans to feign PTSD assumes that fabricated presentations of PTSD in clinical settings arise from well-adjusted, well-informed individuals and makes no distinction between malingering and factitious presentations. While both of the studies we have mentioned acknowledged the need to replicate their results with clinical populations presenting with fabricated PTSD, there are no reports to date on research that has done this.

The present study represents an attempt to assess realistically the usefulness of the MMPI in differentiating Vietnam combat veterans with PTSD from veterans with fabricated PTSD symptoms and from Vietnam veterans with other psychiatric disorders. Given the convincing evidence for symptom overreporting in Vietnam veterans with PTSD (6–9), if veterans with fabricated symptoms are in fact a heterogeneous group, then the previous successes in using the MMPI F scale and PTSD subscale for detecting factitious presentations are not likely to be replicated in a clinical population.

## METHOD

The subjects were 39 veterans who had served in Vietnam who were referred to a partial hospitalization program for evaluation and treatment during a 12-month period from 1985 to 1986. These included 13 veterans with combat-related PTSD (randomly selected from a group of 47 veterans with PTSD who were referred during this period), 13 veterans with psychiatric disorders other than PTSD (randomly selected from 16 such veterans referred during this period), and 13 veterans who were judged to be presenting fabricated symptoms of PTSD (all such veterans referred during this period). It was verified that all 39 veterans had served in Vietnam and had at least some possible exposure to combat conditions; however, their actual combat exposure varied considerably.

The subjects were evaluated and given diagnoses by three clinicians (a clinical psychologist, a psychiatrist, and a clinical nurse) following a structured interview derived from the *DSM-III* criteria. The veterans were evaluated with respect to presenting symptoms, motivation for treatment, treatment history, service history, and premorbid history. Service in Vietnam under possible combat conditions was verified through use of service discharge papers, claims folders, and military history reports when available.

The veterans' combat exposure was rated by the interviewers on a scale from 0 (no direct exposure to combat or life-threatening conditions) to 3 (heavy combat and exposure to life-threatening conditions). These ratings were derived, by agreement of all three clinicians, from the veterans' reports of combat exposure and job assignment combined with their confirmed military occupational specialty and assignment to direct combat, combat support, or noncombat units. Each veteran was given the MMPI after completion of the interview evaluation and before he participated in the treatment program.

After completing the MMPI, all 39 veterans participated in a partial hospitalization program for Vietnam veterans. This group therapy program has been described in detail elsewhere (11). The veterans participated 3 days per week, 4–6 hours daily, in a variety of therapeutic activities. During this time individual assessment of motivation for treatment and presentation of symptoms continued.

On the basis of the interview assessment and ongoing treatment evaluations, the veterans were classified into three groups of 13: PTSD, non-PTSD psychiatric, and fabricated PTSD. Veterans in the PTSD group were judged by the three clinicians to meet criteria for the diagnosis according to *DSM-III*; it was determined that all 13 had experienced moderate to heavy combat exposure and stressors. The non-PTSD psychiatric group were Vietnam combat veterans who presented for treatment with symptoms of psychiatric disorders other than PTSD and did not meet criteria for this disorder. Of these veterans, five were given diagnoses of dysthymic disorder, two bipolar affective disorder, two borderline personality disorder, one passive-aggressive personality disorder, and three schizophrenic disorders.

Veterans identified by all three clinicians as presenting fabricated symptoms were included in the third group. These veterans were generally rated as having had minimal combat exposure and were identified as either fabricating combat experiences (verified by confession or confrontation in therapy or by presentation of clearly exaggerated and conflicting historical information) or presenting inconsistent and transient symptoms with clearly identified secondary gain (e.g., anxiety symptoms that disappeared when the veteran believed he was unobserved). Of the veterans included in this group, five sought treatment while their criminal trials were pending (one for arson, one for spousal assault, one for robbery, and two for pedophilia), and six sought treatment after filing appeals of rejected compensation claims for PTSD. Two other veterans presented tales of clearly exaggerated and conflicting combat experiences and symptoms, but no clear primary gain could be identified (thus, they met the criteria for factitious disorder).

## RESULTS

The subjects in the study ranged in age from 34 to 42 years, with an average of 37.8. The mean±SD age was 37.6±2.1 for subjects in the PTSD group, 37.8±2.6 for the group with other psychiatric disorders, and 38.1±2.3 for the fabricated PTSD group. Analysis of variance (ANOVA) revealed no significant differences in age between the groups ($F=0.13$, $df=2, 37$, $p>0.10$).

The three groups had significantly different ratings

**TABLE 1. Scores on MMPI Scales of 39 Vietnam Veterans With PTSD, Other Psychiatric Disorders, or Fabricated Symptoms of PTSD**

| MMPI Scale | PTSD (N=13) Mean | PTSD (N=13) SD | Other Psychiatric Disorders (N=13) Mean | Other Psychiatric Disorders (N=13) SD | Fabricated Symptoms (N=13) Mean | Fabricated Symptoms (N=13) SD | Analysis of Variance F (df=2, 37) | Analysis of Variance p |
|---|---|---|---|---|---|---|---|---|
| PTSD | 35.0 | 8.3 | 27.5 | 12.2 | 31.7 | 13.8 | 1.36 | 0.27 |
| L | 48.8 | 6.9 | 45.5 | 4.7 | 48.2 | 7.5 | 0.94 | 0.39 |
| F | 81.2 | 15.4 | 73.1 | 15.8 | 81.0 | 19.3 | 1.03 | 0.36 |
| K | 46.8 | 9.6 | 43.3 | 6.8 | 45.6 | 10.2 | 0.50 | 0.61 |
| Hs | 81.3 | 14.9 | 68.4 | 17.9 | 76.8 | 23.3 | 1.53 | 0.23 |
| D | 97.9 | 14.5 | 83.8 | 14.8 | 85.5 | 20.2 | 2.73 | 0.08 |
| Hy | 77.7 | 10.6 | 66.1 | 12.3 | 72.4 | 15.2 | 2.60 | 0.09 |
| Pd | 86.5 | 15.4 | 76.2 | 14.4 | 76.8 | 14.3 | 2.10 | 0.13 |
| Mf | 66.4 | 7.4 | 63.7 | 6.3 | 59.3 | 5.0 | 4.07 | 0.02 |
| Pa | 84.4 | 10.9 | 67.5 | 17.3 | 76.3 | 17.6 | 3.71 | 0.03 |
| Pt | 92.4 | 9.9 | 78.5 | 14.9 | 81.3 | 17.3 | 3.30 | 0.05 |
| Sc | 102.5 | 13.5 | 84.0 | 23.6 | 92.1 | 26.8 | 2.23 | 0.12 |
| Ma | 65.8 | 12.0 | 63.1 | 11.7 | 69.5 | 12.7 | 0.86 | 0.43 |
| Si | 69.8 | 10.9 | 70.1 | 8.3 | 63.6 | 15.2 | 1.24 | 0.30 |

of combat exposure: mean±SD=2.85±0.38 for the PTSD group, 1.77±0.83 for the non-PTSD psychiatric group, and 1.15±0.38 for the fabricated PTSD group ($F=29.37$, $df=2, 37$, $p<0.001$). Tukey post hoc analyses revealed these differences to be significant for all three groups ($p<0.05$).

Table 1 presents the total (T) scores on each of the MMPI validity and clinical scales and the raw scores on the MMPI PTSD subscale. A one-way multivariate analysis of variance (MANOVA) using Wilks' lambda revealed no significant group effect for the MMPI test variables (multivariate $F=1.13$, $df=23, 46$, $p>0.10$). However, to fully examine the sensitivity of the MMPI (in particular the MMPI F scale and PTSD subscale) to possible group differences, univariate ANOVAs were calculated for each of the MMPI scale scores. Significant effects were followed by Tukey post hoc tests. These results are also included in table 1.

Table 1 shows no significant differences on either the MMPI PTSD subscale or the MMPI F scale. In fact, the mean F scale scores for the PTSD and fabricated PTSD groups were nearly identical. Significant differences were found in the ANOVAs for the MMPI masculinity-femininity (Mf), paranoia (Pa), and psychasthenia (Pt) scales. Post hoc analyses revealed that the PTSD group scored significantly higher ($p<0.05$) on the Pa scale than the psychiatric group but not the fabricated PTSD group. Despite the significant ANOVA, post hoc analysis revealed no differences between the three groups on the scale. Only on the Mf scale did the PTSD group significantly differ ($p<0.05$) from the fabricated PTSD group. Of additional interest in table 1 are the higher standard deviations for the fabricated PTSD group than for the other two groups on all but two variables, suggesting greater variability in their responses to the MMPI.

Three separate direct discriminant analyses were performed to predict group membership. Table 2 shows the results of the analysis with MMPI F scale T scores and MMPI PTSD subscale raw scores as predictors. Inspection of this table reveals that these variables correctly classified only 17 of the 39 veterans, or 43.59%, which is only slightly better than could have been obtained by chance. Given that the MANOVA for the MMPI test variables did not reveal a significant effect, the subsequent significant effects found in the univariate ANOVAs must be regarded as quite tenuous. Thus, no further discriminant analyses using these variables were deemed appropriate.

**TABLE 2. MMPI Classification of 39 Vietnam Veterans Clinically Diagnosed as Having PTSD, Other Psychiatric Disorders, or Fabricated Symptoms of PTSD**

| | Classification According to MMPI | | | | | |
|---|---|---|---|---|---|---|
| | PTSD | | Other Psychiatric Disorders | | Fabricated Symptoms | |
| Clinical Diagnosis | N | % | N | % | N | % |
| PTSD (N=13) | 8 | 61.54 | 2 | 15.38 | 3 | 23.08 |
| Other psychiatric disorders (N=13) | 3 | 23.08 | 7 | 53.85 | 3 | 23.08 |
| Fabricated symptoms (N=13) | 6 | 46.15 | 5 | 38.46 | 2 | 15.38 |
| Total (N=39) | 17 | 43.59 | 14 | 35.90 | 8 | 20.51 |

## DISCUSSION

As anticipated, the results of this study failed to replicate the findings of Fairbank et al. (4) and McCaffrey and Bellamy-Campbell (5). In a clinical population consisting of Vietnam veterans with PTSD, veterans with non-PTSD psychiatric disorders, and veterans with fabricated PTSD symptoms, scores on the MMPI F scale and PTSD subscale proved to be of no value in discriminating real from fabricated PTSD. In fact, this study found no differences between any of the groups on these measures. Only on the MMPI Mf scale did the

fabricated PTSD group differ from the PTSD group, a result that was not predicted and is not explainable at present.

Overall, the results were not surprising given previous evidence of overreporting on the MMPI by Vietnam veterans (7). Consistent with this, the PTSD group obtained higher (although not significantly) mean T scores on 12 of the 13 MMPI scales.

The failure to replicate the findings of the previous studies using a clinical population suggests that using well-adjusted subjects to feign symptoms of PTSD for purposes of psychometric test differentiation has little clinical merit. As suggested previously, this procedure assumes that patients who present fabricated symptoms of PTSD are in fact well-informed and will thus use well-informed falsification strategies. Second, it fails to recognize that the population of veterans presenting fabricated symptoms may be quite heterogeneous, with a wide variety of reasons for feigning illness and, possibly, a wide variety of secondary psychiatric disorders. This explanation is supported by the fact that the fabricated symptoms group in this study obtained the highest variability overall in MMPI scale scores among the three groups.

In conclusion, it appears that the promising results reported in previous attempts to discriminate fabricated PTSD from PTSD by using scores on the MMPI F scale and PTSD subscale are limited to the special nonclinical samples described in those studies, i.e., well-adjusted veterans and mental health professionals feigning PTSD. In clinical application there is apparently no substitute for careful evaluation, observation, and validation of PTSD symptom presentations. This study, consistent with others (12), found that the degree of combat exposure is highly associated with the diagnosis of PTSD, and this remains one of the best predictors of the disorder. It may be that the most effective tools for detecting fabricated symptoms of PTSD are those which verify and quantify combat exposure, such as discharge papers, combat histories, and military records.

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# Developmental History and Object Relations in Psychiatrically Disturbed Adolescent Girls

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*This study explored empirically the relationship between developmental history variables and several dimensions of object relations in a sample of 36 female adolescent inpatients. The results document the importance of preoedipal experience, the relationship with the mother, and continuity of attachments in shaping object relations. In addition, the data point to the importance of distinguishing different dimensions of object relations, such as the affective quality of the object world and the logic and accuracy of attributions, which may have different developmental correlates. The findings also suggest the impact of sexual abuse, typically a postoedipal experience, on enduring object-relational processes.*

(Am J Psychiatry 1990; 147:1061–1068)

Clinicians and researchers (1) have speculated for years on the role of developmental history factors and traumatic events in the genesis of severe psychopathology. Freud initially implicated sexual trauma in the etiology of hysteria but later came to emphasize the role of fantasy. Bolstered by observation of children with disrupted attachment histories (2) and by relevant primate evidence, object relations theorists came to focus again on the impact of real deprivation in infancy and childhood. Winnicott (3) and Kohut (4) focused on failures in maternal responsiveness; Bowlby (5) implicated disruptions in the attachment relationship.

Research on patients with severe personality disorders, particularly borderline patients, has begun to document the role of experiences such as early loss, multiple and changing caretakers, violence, alcoholism, family chaos, and neglect in the genesis of these disorders (6–9). Several studies have established a link between borderline personality disorder and sexual abuse in adult and adolescent samples (8, 10–12).

Presumably, chronic pathogenic experiences and traumatic events in childhood should have an enduring and systematic impact on later patterns of object relations, although this has received little empirical attention. Studies to date on the influence of parental psychopathology and maltreatment on social cognition, which is theoretically of relevance to dimensions of object relations (13), have not, by and large, yielded positive findings (14). Research on adult attachment, particularly by Main and colleagues (15), has begun documenting the relationship between a mother's attachment status (the security of her attachment to her own mother) and the attachment status of her child and have found that securely attached mothers are more likely to have securely attached children. This is one of the few areas of empirical research that has tested the relationship between developmental experience and ways of experiencing relationships.

The present study attempted to explore empirically the relationship between developmental history variables and object relations in a sample of psychiatrically disturbed adolescents. "Object relations" refers, most broadly, to enduring patterns of interpersonal behavior and to the cognitive and affective processes mediating functioning in close relationships. The present study focused on the internal (cognitive and affective) dimensions of object relations, rather than on their behavioral expression. We hypothesized, first, that the presence of developmental history variables such as maternal separations, neglect, physical and sexual abuse, and parental psychopathology should predict more pathological object relations in adolescence and second, that preoedipal risk factors and disrupted attachments should be particularly predictive. We also predicted that different experiences should affect different dimensions of object relations. For example, one might suspect that sexual abuse would lead to a more malevolent object world, since caretakers would be likely to be experienced as hostile and unprotective, and a sense of basic trust (16) would be difficult to maintain. Grossly inconsistent parental behavior, as might occur with alcoholic parents, might be expected to lead to difficulties making logical and accurate attributions of the causes of people's behavior. Because this is a pre-

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Supported by grants from the Department of Psychiatry, the University Center for the Child and the Family, and the Faculty Fund, Department of Psychology, University of Michigan.

liminary study, we did not make specific hypotheses along these lines.

## METHOD

Subjects were 36 female adolescents who were psychiatrically hospitalized at a major medical center and originally selected as part of a study comparing adolescents with borderline personality disorder to other psychiatrically disturbed adolescents on a number of dimensions (9, 11, 17). Patients with chronic psychosis, evidence of gross neuropathology, IQ below 70, or medical problems that would complicate diagnosis or psychological testing were excluded from the study. Subjects received a number of *DSM-III* and *DSM-III-R* discharge diagnoses, including borderline personality disorder, mood disorder, anorexia nervosa, bulimia, and other personality disorders. Subjects ranged in age from 14 to 18 years (mean±SD=15.60±0.99).

A number of developmental history variables were scored by chart review by a trained rater. The rater was blind to the psychological testing data from which object-relational variables were assessed. Patients were typically hospitalized for several months, so chart information was reasonably thorough. For each chart the rater read the intake summary, discharge summary, individual therapist's process notes, case conference report, first 2 weeks of nursing notes, neuropsychological testing reports (if available), information from previous therapists and hospitalizations, school reports, and court reports (if available). Charts were rated for variables assessing the genetic family history; childhood symptoms of the patient; neurological history of the patient; and a variety of traumatic events, including documented neglect, physical and sexual abuse (fondling or penetration), extrusion from the home (being removed or "kicked out" of the residence of the primary caretaker), grossly inappropriate parental behavior (such as a parent double-dating with the child and being sexually provocative with the date), and significant separations, including death, divorce, adoption, prolonged separations from primary caretakers, and foster care history. The variables were coded as present only if there was conclusive evidence. It is therefore very likely that these data contain few false positive codes and relatively more false negatives. Although the data were largely factual and required little inference, a check was undertaken to ensure reliable coding. A second coder blindly rescored all variables on a small sample of subjects; the two coders achieved perfect agreement on 89% of the scores.

Object relations were assessed from Thematic Apperception Test (TAT) responses, using a procedure developed by Westen and colleagues (18). The TAT is a projective test in which subjects make up stories about characters depicted in ambiguous social scenes. It is a useful source of data for assessing object relations because, in describing characters and social episodes, subjects apply their understanding and experience of relationships and people. Administration of the TAT to this sample is described more fully elsewhere (17). Testers asked subjects to tell a story, including what was happening in the picture, what led up to it, the outcome, and what the characters were thinking and feeling. Testers were not familiar with the hypotheses or measures used in this study. The present study examined responses to six cards: cards 1, 2, 3, 4, 13MF, and 15.

Responses to the six TAT cards were coded by using a multidimensional measure of object relations for use with the TAT. This measure assesses four aspects of object relations: complexity of representations of people (the extent to which the subject ascribes complex dispositions to characters whose perspectives are clearly differentiated), affect-tone of relationship paradigms (the affective quality of the object world, from malevolent to benevolent), capacity for emotional investment in relationships and moral standards (the extent to which the person transcends a need-gratifying interpersonal orientation), and understanding of social causality (the extent to which attributions of causality in the social realm are accurate, complex, and psychologically minded). As depicted in table 1, each scale has five levels; level 1 represents the lowest level response and level 5, the highest.

Several recent studies have attempted to validate these scales on a number of samples (19, 20). In normal and clinical samples the measures have predicted both self-reported and clinician-reported social adjustment, as well as scores on relevant subscales (such as hostility, paranoia, and interpersonal sensitivity) of the SCL-90-R (21). Research with a normal sample documented significant correlations between these measures and analogous measures developed for use with interview data, such as psychiatric interviews and psychotherapy transcripts (e.g., the extent to which subjects manifest a malevolent object world in describing TAT characters correlates with the malevolence of their descriptions of actual relationship episodes; see reference 20). This research also found predicted correlations between these measures and theoretically related validated instruments such as Loevinger's test of ego development (22) and Blatt et al.'s measure of qualitative aspects of parental representations (23). For example, Loevinger's measure of ego development, which primarily assesses more affective dimensions such as the experience of relationships as exploitative, correlates with affect-tone of relationship paradigms and capacity for emotional investment in relationships. Complexity of free-response descriptions of significant others, through use of the Blatt measure, correlates with both complexity of representations and social causality as assessed from TAT responses. It has been demonstrated that mean scores (treated as continuous data) and percentage of level 1 responses (hypothesized to be pathological) on all four scales distinguish borderline subjects from psychiatric and normal comparison subjects in both adolescent (17) and adult (13) samples. Two studies just completed (see reference 24)

**TABLE 1. Summary of Measures of Four Aspects of Object Relations**

| Item | Complexity of Representations of People | Affect-Tone of Relationship Paradigms | Capacity for Emotional Investment | Understanding of Social Causality |
|---|---|---|---|---|
| Principle | Scale measures the extent to which the subject clearly differentiates the perspectives of self and others: sees the self and others as having stable, enduring, multidimensional dispositions; and sees the self and others as psychological beings with complex motives and subjective experience. | Scale measures affective quality of representations of people and relationships. It attempts to assess the extent to which the person expects from the world, and particularly the world of people, profound malevolence or overwhelming pain or views social interaction as basically benign and enriching. | Scale measures the extent to which others are treated as ends rather than means, events are regarded in terms other than need gratification, and moral standards are developed and considered. | Scale measures the extent to which attributions about the causes of people's actions, thoughts, and feelings are logical, accurate, complex, and psychologically minded. |
| Level 1 | People are not clearly differentiated: confusion of points of view | Malevolent representations: gratuitous violence or gross negligence by significant others | Need-gratifying orientation; profound self-preoccupation | Noncausal or grossly illogical depictions of psychological and interpersonal events |
| Level 2 | Simple, unidimensional representations; focus on actions; traits are global and univalent | Representation of relationships as hostile, empty, or capricious but not profoundly malevolent; profound loneliness or disappointment in relationships | Limited investment in people, relationships, and moral standards; conflicting interests recognized, but gratification remains primary aim; moral standards primitive and unintegrated or followed to avoid punishment | Rudimentary understanding of social causality; minor logic errors or unexplained transitions; simple stimulus-response causality |
| Level 3 | Minor elaboration of mental life or personality | Mixed representations with mildly negative tone | Conventional investment in people and moral standards; stereotypic compassion, mutuality, or helping orientation; guilt at moral transgressions | Complex, accurate situational causality and rudimentary understanding of the role of thoughts and feelings in mediating action |
| Level 4 | Expanded appreciation of complexity of subjective experience and personality dispositions; absence of representations integrating life history, complex subjectivity, and personality processes | Mixed representations with neutral or balanced tone | Mature, committed investment in relationships and values: mutual empathy and concern; commitment to abstract values | Expanded appreciation of the role of mental processes in generating thoughts, feelings, behaviors, and interpersonal interactions |
| Level 5 | Complex representations indicating understanding of interaction of enduring and momentary psychological experience; understanding of personality as system of processes interacting with each other and the environment | Predominantly positive representations; benign and enriching interactions | Autonomous selfhood in the context of committed relationships; recognition of conventional nature of moral rules in the context of carefully considered standards or concern for concrete people or relationships | Complex appreciation of the role of mental processes in generating thoughts, feelings, behaviors, and interpersonal interactions; understanding of unconscious motivational processes |

found predicted developmental differences between second and fifth graders and between early and late adolescents. Together, these studies suggest that TAT responses can provide an index of certain dimensions of object relations.

TAT responses were coded by two advanced graduate students in clinical psychology and three research assistants with bachelor's degrees. All cards were double-coded independently by two raters. The stories provided to coders were typed one to a page in random order, so that rating of multiple stories in the same protocol would be entirely independent. Reliability was computed by using the intraclass correlation coefficient, with the Spearman-Brown correction for multiple coding. Uncorrected reliabilities ranged from 0.71 to 0.96. Corrected reliabilities were as follows: affect-tone, 0.91; complexity of representations, 0.96; capacity for emotional investment, 0.83; and social causality, 0.94.

## RESULTS

Table 2 reports significant findings on the relationship between object relations and parental pathology. The table presents mean scores on each of the four

**TABLE 2. Parental Pathology, Traumatic Childhood Experiences, and Scores on Four Scales Assessing Object Relations for 36 Psychiatrically Disturbed Adolescent Girls**

| | | Affect-Tone of Relationship Paradigms | | | Complexity of Representations of People | | | Capacity for Emotional Investment | | | Understanding of Social Causality | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Score | | | Score | | | Score | | | Score | | |
| Item | N | Mean | SD | Malevolent Responses (%) | Mean | SD | Poorly Differentiated Responses (%) | Mean | SD | Need-Gratifying Responses (%) | Mean | SD | Grossly Illogical Responses (%) |
| Parental pathology | | | | | | | | | | | | | |
| Maternal psychiatric illness | | | | | | | | | | | | | |
| Yes | 21 | 2.33 | 0.50 | —[a] | — | — | — | 1.81 | 0.50 | 38.80 | — | — | 18.80 |
| No | 74 | 2.65 | 0.69 | — | — | — | — | 2.15 | 0.51 | 20.10 | — | — | 2.40 |
| t | — | 1.64[b] | — | — | — | — | — | 1.96[b] | — | 1.67[b] | — | — | 2.17[b] |
| Maternal alcohol abuse | | | | | | | | | | | | | |
| Yes | 8 | — | — | — | — | — | 8.10 | — | — | — | — | — | 25.80 |
| No | 27 | — | — | — | — | — | 0.10 | — | — | — | — | — | 8.60 |
| t | — | — | — | — | — | — | 2.14[b] | — | — | — | — | — | 1.79[b] |
| Paternal psychiatric illness | | | | | | | | | | | | | |
| Yes | 23 | — | — | — | — | — | — | — | — | — | 1.99 | 0.44 | 17.20 |
| No | 12 | — | — | — | — | — | — | — | — | — | 2.27 | 0.28 | 2.80 |
| t | — | — | — | — | — | — | — | — | — | — | 2.00[b] | — | 1.80[b] |
| Paternal criminality | | | | | | | | | | | | | |
| Yes | 7 | — | — | — | — | — | 9.30 | — | — | — | — | — | — |
| No | 28 | — | — | — | — | — | 0.90 | — | — | — | — | — | — |
| t | — | — | — | — | — | — | 2.42[c] | — | — | — | — | — | — |
| Childhood experiences | | | | | | | | | | | | | |
| Neglect | | | | | | | | | | | | | |
| Yes | 11 | 2.20 | 0.51 | — | — | — | — | — | — | — | — | — | — |
| No | 25 | 2.58 | 0.59 | — | — | — | — | — | — | — | — | — | — |
| t | — | 1.85[b] | — | — | — | — | — | — | — | — | — | — | — |
| Grossly inappropriate parenting | | | | | | | | | | | | | |
| Yes | 9 | — | — | — | 2.78 | 0.73 | — | — | — | — | — | — | — |
| No | 27 | — | — | — | 2.26 | 0.42 | — | — | — | — | — | — | — |
| t | — | — | — | — | −2.67[c] | — | — | — | — | — | — | — | — |
| Maternal separation | | | | | | | | | | | | | |
| Yes | 12 | 2.15 | 0.49 | — | 2.18 | 0.42 | — | — | — | — | 1.83 | 0.40 | 26.80 |
| No | 24 | 2.61 | 0.58 | — | 2.50 | 0.59 | — | — | — | — | 2.19 | 0.37 | 6.60 |
| t | — | 2.42[c] | — | — | 1.66[b] | — | — | — | — | — | 2.67[d] | — | 2.59[d] |
| Paternal separation | | | | | | | | | | | | | |
| Yes | 17 | — | — | — | — | — | — | 1.79 | 0.54 | 41.60 | — | — | — |
| No | 18 | — | — | — | — | — | — | 2.13 | 0.49 | 19.80 | — | — | — |
| t | — | — | — | — | — | — | — | 1.98[b] | — | 1.99[b] | — | — | — |
| Adoption | | | | | | | | | | | | | |
| Yes | 3 | 1.77 | 0.85 | 56.10 | — | — | 21.70 | — | — | 54.40 | 1.58 | 0.22 | 47.80 |
| No | 31 | 2.58 | 0.50 | 15.40 | — | — | 1.60 | — | — | 24.30 | 2.13 | 0.37 | 8.30 |
| t | — | 2.55[b] | — | 1.57[e] | — | — | 4.21[e] | — | — | 1.67[b] | 2.52[d] | — | 3.55[e] |
| Extrusion from home | | | | | | | | | | | | | |
| Yes | 8 | — | — | — | — | — | 8.10 | — | — | — | — | — | — |
| No | 28 | — | — | — | — | — | 1.80 | — | — | — | — | — | — |
| t | — | — | — | — | — | — | 1.79[b] | — | — | — | — | — | — |
| Sexual abuse | | | | | | | | | | | | | |
| Yes | 10 | 2.48 | 0.52 | — | — | — | — | — | — | — | — | — | — |
| No | 21 | 2.64 | 0.58 | — | — | — | — | — | — | — | — | — | — |
| t | — | 1.80[b] | — | — | — | — | — | — | — | — | — | — | — |
| Mother physically abusive | | | | | | | | | | | | | |
| Yes | 4 | 1.97 | 0.64 | 40.00 | — | — | 16.20 | — | — | — | — | — | 27.50 |
| No | 31 | 2.57 | 0.57 | 16.70 | — | — | 1.70 | — | — | — | — | — | 7.50 |
| t | — | 1.93[b] | — | 2.01[b] | — | — | 3.14[d] | — | — | — | — | — | 1.88[b] |
| Psychological father physically abusive | | | | | | | | | | | | | |
| Yes | 13 | 2.16 | 0.44 | — | — | — | — | — | — | — | — | — | — |
| No | 22 | 2.60 | 0.61 | — | — | — | — | — | — | — | — | — | — |
| t | — | 2.14[b] | — | — | — | — | — | — | — | — | — | — | — |

[a]Dashes indicate nonsignificant differences. All data analyzed by t test, df=29–35 (depending on missing data), two-tailed for grossly inappropriate parenting, one-tailed elsewhere.
[b]$p \leq 0.05$.
[c]$p \leq 0.01$.
[d]$p \leq 0.005$.
[e]$p \leq 0.001$.

scales as well as the percent of level 1 (pathological) responses on each scale (percentage of malevolent, profoundly egocentric or poorly differentiated, need-gratifying, and grossly illogical responses). Several dimensions of parental pathology were associated with more pathological object relations in adolescent sub-

**TABLE 3. Correlations Between Social History Variables and Scores on Four Scales Assessing Object Relations for 36 Psychiatrically Disturbed Adolescent Girls**

| Item | Affect-Tone of Relationship Paradigm | | Complexity of Representations of People | | Capacity for Emotional Investment | | Understanding of Social Causality | |
|---|---|---|---|---|---|---|---|---|
| | r | Malevolent Responses (%) | r | Poorly Differentiated Responses (%) | r | Need-Gratifying Responses (%) | r | Grossly Illogical Responses (%) |
| Number of family moves | −0.25 | —[a] | — | — | — | — | −0.22 | 0.29 |
| Number of mother surrogates | −0.46[b] | 0.48[b] | −0.22 | 0.21 | −0.29 | 0.26 | — | — |
| Duration of sexual abuse (N=12) | −0.37 | 0.29 | — | 0.70[c] | −0.32 | 0.38 | −0.22 | 0.40 |
| Number of preoedipal risk factors | −0.45[c] | 0.44[c] | −0.23 | 0.38[d] | −0.43[c] | 0.37[d] | −0.25 | — |

[a]Dashes indicate nonsignificant values. All data analyzed by Pearson's r.
[b]$p \leq 0.005$.
[c]$p \leq 0.01$.
[d]$p \leq 0.05$.

jects, and different parental variables were linked to different object-relational dimensions. Maternal psychiatric illness was the best predictor of pathological object relations; presence of maternal pathology was associated with greater pathology on every scale except complexity of representations.

Table 2 also reports the relationship between object relations and traumatic childhood experiences. Once again, several developmental variables predicted disturbed object relations in adolescent subjects, and some variables were quite specific to particular dimensions. Maternal separation appears to have a pervasive effect on object relations. Adopted subjects in this study also showed more deficits in object relations, although the number of adopted subjects was very small. As could be expected, sexual abuse had a primary impact on affect-tone of relationship paradigms.

Table 3 shows the correlations between object relations and several social history variables scored as continuous data. The number of mother surrogates was strongly correlated with malevolence of affect-tone but also predicted pathological object relations more generally. Despite the small sample size of sexually abused subjects (N=12), a striking correlation emerged between duration of sexual abuse (measured in months) and the percentage of poorly differentiated representations. Duration of sexual abuse correlated with mean scores or percentage of level 1 scores on every scale.

To test the theory that the preoedipal years are a critical period for object relations, or at the very least that these years are particularly important in shaping enduring object-relational patterns, we compiled two composite indices. One was of the number of preoedipal risk factors present (including premature delivery, report of "difficult" infancy, separations and losses, abuse, and maternal borderline personality disorder, which has been hypothesized to be particularly disruptive during the preoedipal years), and the other was an analogous index of latency risk factors (including learning disability, separations and losses, and abuse). The number of latency risk factors did not significantly predict any dimension of object relations; however, as can be seen in table 3, the number of preoedipal risk factors correlated in the predicted direction with every dimension. A stepwise multiple regression predicting mean object relations across the four scales, from scores on these two composite variables and composite measures of maternal and paternal pathology, found that preoedipal risk factors were the sole predictive variable, with a partial coefficient (r) for this variable of −0.50 ($p=0.003$). The relationship between the preoedipal risk variable and various indices of object relations remained robust even after removal of premature delivery (a preoedipal variable not typically described as related to object-relational pathology) and maternal borderline personality disorder (which is arguably not a phase-specific pathogen).

Several other findings are of note. Premature delivery significantly predicted complexity and emotional investment scores, and history of diagnosed learning disability predicted malevolent affect-tone, although the small number of cases and difficulty coding these variables warrant caution in generalizing. As a secondary analysis, we also analyzed percent of high scores on each scale (scored as level 4 or 5). These findings, unlike the previous results, were not based on a priori hypotheses and should thus be taken with caution unless they are highly significant, as several are. The relationship between maternal psychiatric illness (scored as present or absent) and affect-tone was accounted for in large measure by differences in the percentage of high-level responses manifest across the subject's protocol (8.5% for those with maternal psychiatric illness versus 26.3% for those without; $t=3.01$, $df=34$, $p=0.0002$). A similar pattern emerged for presence of maternal depression and alcohol abuse (both significant at $p<0.05$). A surprising finding emerged with respect to maternal physical abuse: abused subjects manifested significantly *more* high-level responses on complexity of representations than nonabused subjects (31.2%

versus 8.1%; $t=-3.49$, $df=33$, $p=0.02$, two-tailed). Presence of grossly inappropriate parental behavior was similarly associated with a higher percentage of high-level responses on complexity of representations (26.3% for those with such behavior versus 5.2% for those without it; $t=3.36$, $df=34$, $p=0.002$, two-tailed). Presence of an abusive psychological father (that is, the male parent who lived in the home most while the patient was a child and who may or may not have been the biological father) was associated with fewer high-level responses on affect-tone (4.5% for those with such a father versus 21.9% for those without such a father; $t=2.63$, $df=34$, $p=0.005$).

Also of note were findings with respect to subjects' ages at particular traumatic experiences. Analysis of variance documented that adoption *after* the first 3 months accounted for the differences between adopted and nonadopted subjects; for affect-tone, for example, $F=6.74$, $df=2, 31$, $p=0.004$. Age at maternal separation (coded as age 0–4, 5–11, 12–18 years, and none, since exact ages were sometimes difficult to ascertain) predicted affect-tone and percent of grossly illogical responses in a linear fashion, such that earlier separation was associated with more pathological object relations (affect-tone, $r=0.40$, $N=12$, $p=0.02$; percent of grossly illogical responses, $r=-0.42$, $N=12$, $p=0.01$). Finally, the earlier the physical abuse by the mother, the more level 1 responses were found on every scale except affect-tone; for example, for percent of poorly differentiated responses on the complexity scale, $F=10.46$, $df=3, 29$, $p=0.0001$.

## DISCUSSION

Although the developmental history data are retrospective and thus cannot directly demonstrate causality, the temporal relationship between prior experiences and current object relations makes inferences about causality appropriate. Maternal psychiatric illness appeared to have a pervasive effect on most of the dimensions of object relations studied here, as did maternal alcohol abuse. Prolonged separations from the mother were also strongly predictive of pathology on all four dimensions, as was the number of mother surrogates on three of the four measures. Although paternal pathology of various sorts was associated with specific object relational difficulties in adolescence, the pattern of specific findings is not easily explained; and in general, paternal variables were far less predictive than maternal ones (e.g., number of father surrogates and paternal separations had no relationship to object-relational difficulties, in comparison to strong associations with the analogous maternal variables). These findings support the psychoanalytic assumption of a critical role of the mother and of disrupted attachments in the genesis of object-relational pathology. Further, the generally strong correlations between number of preoedipal risk factors and all four dimensions of object relations, and the absence of such correlations with latency risk factors, provide clear support for the critical role of preoedipal experience in shaping object relations; this finding is supported by the regression analysis.

Affect-tone of relationship paradigms, in particular, was uniformly associated with history of maternal difficulties, preoedipal risk factors, and disrupted attachments (particularly the number of mother surrogates and adoption after 3 months of age). Children whose mothers are psychiatrically disturbed, who have problematic preoedipal relationships and experiences, or who are confronted with frequent maternal separations and are forced to accept many different mother surrogates over time apparently develop the expectation that intimate relationships are not safe and nurturant. Maternal psychiatric illness, alcohol abuse, and depression had a specific depressing effect on percentage of high-level affect-tone responses, suggesting that the children of pathological mothers have more difficulty forming and retrieving relatively benign and benevolent representations. It should be noted that while these findings are supportive of the psychoanalytic hypothesis of the importance of preoedipal experience for subsequent object relations, they do not directly support a developmental arrest or deficit model. Malevolent expectations are an abnormality, not an arrest at an early stage of normative development, and future models of object relations will need to provide a more complex account of the interplay among deficits, conflicts, and social learning in the etiology of object-relational pathology (25, 26).

The findings also point to the importance of distinguishing several interrelated but distinct dimensions of object relations (24–26), since these may have very different developmental correlates. Predictably, a history of neglect was associated with a more malevolent object world. Neglect, like history of maternal separation, was also associated with a higher percentage of illogical attributions. This suggests that the adolescents whose mothers were neglectful or inexplicably absent for periods of months or years (which often occurred many times) later have difficulty making sense of why people do what they do and tend to make very idiosyncratic attributions. This finding may be related to Main et al.'s research on infants with a "disorganized" pattern of attachment (27), whose "internal working models" of the attachment relationship do not permit them to know which way to act with their mothers and what to expect. The number of times the family moved, which is probably a good index of family chaos or, at the least, of a disruptive environment, also correlated with both mean affect-tone scores and percentage of grossly illogical responses and mean causality scores, again suggesting that adolescents from disrupted households have difficulty making sense of the social world and have more malevolent expectations of relationships; however, these correlations were only trends.

In this study, as in a similar study of adult inpatients (Nigg, Silk, Westen, et al., unpublished data), sexually

abused subjects had a more malevolent object world. The sexual abuse was primarily in the latency years, which suggests that postoedipal events may have an important impact on object relations in a way that has been relatively neglected by psychoanalytic theory (25, 26). Although correlations must be interpreted cautiously because of the small number of subjects who were sexually abused (N=12), the correlation between duration of sexual abuse and object-relational pathology is also striking. Duration of sexual abuse correlated with pathology in every dimension of object relations, with the exception of mean complexity; the most remarkable correlation was with the percentage of poorly differentiated, egocentric responses (level 1 on complexity). These scores are relatively rarely given and reflect severe confusion of perspectives of different people or a poorly bounded sense of identity. It seems likely that this finding is related to the kind of cognitive disruption and identity disturbance that can be produced by repeated experience of overwhelming affect, as in sexual abuse.

The results of this study indirectly support the findings of other research (28–30) documenting the impact of disrupted attachments and generally disruptive family experience on subsequent social functioning. Since object-relational pathology is an integral component of most personality disorders, given the high prevalence of personality disorders among depressed patients (31) and presumably among abusive and neglectful parents, studies of the relationship between parental pathology and psychiatric disorders in offspring should consider dimensions of object relations as both mediating variables and as outcome measures.

More generally, these results represent a preliminary effort to grapple in an empirical way with some thorny questions about the relationship between psychic reality and actual reality with which psychoanalysis has been wrestling for some time (32, 33). The data also bear on epistomological questions about the relationship between causality and meaning (34–36) and suggest the importance of developing theory that attempts to explain the way actual events can causally affect psychological meanings or "psychic reality" and affect attributional processes (such as a malevolent object world or a tendency to interpret other people's behavior idiosyncratically).

It is important to note the limitations of this study. In many respects this was an exploratory study, with a small sample size and unknown applicability to males, nonpsychiatric patients, and adults. Although the findings are compelling, theoretically consistent, and remarkably significant in the light of the small sample size, future studies using larger and more representative samples of adolescents and adults are clearly in order. Subjects selected for the study were not, for example, consecutive admissions, and it is difficult to know what impact sampling bias might have had, although it is difficult to generate a rival hypothesis along these lines that could explain the number and strength of the findings. Since this was an exploratory study with a small sample size, it was also not possible to correct for potentially spurious findings generated by multiple tests without eliminating the possibility of testing any hypotheses. We tried to avoid spurious results, however, by only reporting findings that were theoretically expected, were significant at 0.01 or better, or formed a coherent pattern. Although this clearly suggests the need for caution in generalizing the results, it should be noted that false or chance significant findings should occur in both directions, and that was not the case: presence of pathogenic experiences consistently predicted *more disturbed*, not less disturbed, object relations, as expected, and the composite preoedipal variable was highly predictive, even after partialling out the effects of other independent variables.

A second limitation is that developmental history data were obtained by chart review, which imposes clear limitations on the findings. As noted earlier, however, presence of developmental history variables was coded very conservatively, so that findings that did emerge are in many ways surprising in light of the likelihood of false negatives. Further, chart review data may actually be more useful in this design than interview data, since the same psychological structures and processes that influence responses to the TAT (such as a malevolent object world) could influence memory and reporting of developmental history variables, such as abuse and neglect. A final, and equally important, limitation is that although the TAT measures of object relations have been to some extent validated and documented to distinguish various criterion groups and to predict social adjustment, future research needs to use other measures as well, particularly as applied to psychiatric interview data.

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# Clozapine and Seizures

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*Clozapine is a newly released antipsychotic that is associated with a higher prevalence of seizures than traditional neuroleptics. The authors describe four patients who developed seizure activity during clozapine treatment and provide recommendations for clinical management of this problem.*

(Am J Psychiatry 1990; 147:1069–1071)

Clozapine is an atypical antipsychotic that has been shown to be effective in treating patients with refractory schizophrenia (1, 2) and those with intolerance to currently available psychotropics (3, 4). It also appears to be less likely to cause extrapyramidal symptoms and tardive dyskinesia (2, 5, 6).

The drug's release in the United States was delayed because of its side effect profile. In addition to a 1%–2% incidence of agranulocytosis (6), clozapine has been associated with an unusually high incidence of seizures in patients with no previous history of ictal episodes (6). Seizures occur in approximately 1% of patients treated with antipsychotic drugs (7). The prevalence, however, is higher with clozapine and is dose-dependent. The reported prevalence of seizures with clozapine is 5% for patients treated with 600–900 mg/day, 3%–4% for patients treated with 300–599 mg/day, and 1%–2% for patients treated with less than 300 mg/day (data on file, Sandoz Pharmaceuticals, 1989). The average therapeutic dose of clozapine is 300–450 mg/day, but some patients need as much as 900 mg/day to experience a therapeutic effect.

To our knowledge, there has been only one previous published report of patients who had seizures while taking clozapine (8), and these patients had ingested larger than recommended doses. In this paper we will present the cases of four patients who had seizure activity while taking therapeutic or subtherapeutic doses, and we will present some clinical guidelines for management of this problem based on our experience in an open trial.

## CASE DESCRIPTIONS

At our center, we have prescribed clozapine to 19 patients. Before initiation of a clozapine trial, each patient was given a complete physical examination and laboratory test battery. The patients' current psychotropic drug regimens were gradually discontinued, and clozapine administration began 24 hours after the last dose of other drugs. The clozapine dose was increased by 25 mg/day or less if orthostatic hypotension developed. Before increasing any patient's clozapine dose above 600 mg/day, an EEG was done, and further increases were made only if the EEG was within normal limits.

Four of the 19 patients developed seizure activity. Clinical data on these patients are presented in table 1. The first patient had a relatively uncomplicated course after a single grand mal seizure. She remained seizure-free while taking 600 mg/day of clozapine and 300 mg/day of phenytoin.

After discharge from our facility, patient 2 had three unwitnessed seizures despite supposed compliance with a regimen of clozapine and phenytoin. When he was evaluated at medical emergency rooms, however, his phenytoin blood levels were at times subtherapeutic, suggesting noncompliance. Despite this possibility of intermittent noncompliance, his clozapine dose was further decreased to 450 mg/day. With this decrease and with further education regarding the need for compliance with his medication regimen, he remained seizure-free.

Patient 3 never actually had a seizure. However, myoclonus, frontal release signs, and an abnormal EEG

Received Oct. 13, 1989; revision received Feb. 6, 1990; accepted Feb. 12, 1990. From the Department of Psychiatry, University of California, San Francisco. Address reprint requests to Dr. Haller, 401 Parnassus Ave., San Francisco, CA 94143.

**TABLE 1. Patients Who Developed Seizure Activity While Taking Clozapine[a]**

| Patient | Sex | Age (years) | Past Medical History | Current Medications | Past Treatments | Duration of Clozapine Before Seizure (weeks) | Dose at Seizure (mg/day) |
|---|---|---|---|---|---|---|---|
| 1 | F | 30 | Schizoaffective disorder for 11 years; premature by 2½ months | Lithium carbonate, 450 mg/day; lorazepam, 3 mg/day | Trazodone, buspirone, perphenazine, trifluoperazine, thiothixene, thioridazine, haloperidol | 8.5 | 700 |
| 2 | M | 37 | Chronic undifferentiated schizophrenia for 11 years; polysubstance abuse as teenager (alcohol, marijuana, amphetamines); one grand mal seizure after abrupt discontinuation of maprotiline, none since | Perphenazine, 96 mg/day; diazepam, 2.5 mg/day | Trifluoperazine, chlorpromazine, thiothixene, fluphenazine, haloperidol, loxapine, alprazolam, clonazepam, maprotiline, lithium, reserpine, six ECTs 22 years earlier | 9.0 | 600 |
| 3[b] | F | 30 | Chronic paranoid schizophrenia for 10 years | Haloperidol, 60 mg/day | Trifluoperazine, chlorpromazine, thiothixene, lithium, chlordiazepoxide, clonazepam, alprazolam | 7.0 | 750 |
| 4 | F | 30 | Chronic paranoid schizophrenia for 5 years; preexisting seizure disorder (petit and grand mal seizures since age 15), stable with phenobarbital; polysubstance abuse in past (marijuana, cocaine, alcohol, amphetamines) | Haloperidol, 20 mg/day; trazodone, 300 mg/day; phenobarbital, 270 mg/day | Fluphenazine, thiothixene | 0.5 | 75 |

[a]The indications for clozapine treatment were nonresponse to other treatments (all patients) and inability to tolerate other drugs (patients 1 and 4).
[b]Patient 3 did not actually have a seizure; she experienced myoclonus, decreased speech fluency, and frontal release signs, and her EEG showed hemispheric and generalized spike activity.

indicated neurotoxicity and a possibly decreased seizure threshold. After the clozapine dose was decreased, these symptoms cleared entirely and she remained seizure-free.

Patient 4 agreed to treatment with clozapine, despite a preexisting seizure disorder, after she was informed that she might have a resultant increased vulnerability to seizures. In fact, despite a therapeutic phenobarbital blood level (23 mg/l), she had a generalized grand mal seizure while taking only 75 mg/day of clozapine. Her anticonvulsant regimen was further manipulated to minimize the risk of seizures while maximizing the therapeutic benefit she was experiencing from clozapine. She was ultimately stabilized on a regimen of 325 mg/day of clozapine, 4500 mg/day of valproic acid, and 750 mg/day of primidone, and her anticonvulsant blood levels were in the therapeutic range. (Because of presumed hepatic enzyme induction, an unusually high dose of valproic acid was necessary to achieve a therapeutic blood level of 73 mg/liter.)

## DISCUSSION

No patient in our series who was taking less than 600 mg/day had a seizure except the one patient with a preexisting seizure disorder. Of the eight patients prescribed 600 mg/day or more, three (37.5%) had ictal activity. This dose-dependent relationship is further supported by the fact that these three patients remained seizure-free after their doses were decreased.

To our knowledge, there has been one prior published report of patients who had seizures while taking clozapine (8). The first patient had a seizure 24 hours after a planned dose increase from 800 to 900 mg/day, but further questioning revealed that she had actually

**TABLE 1 (continued)**

| Management and Outcome |
|---|
| Clozapine withheld for 24 hours, loading dose of phenytoin followed by 300 mg h.s., clozapine restarted at 500 mg/day; maintenance treatment=600 mg/day of clozapine+300 mg/day of phenytoin, no further seizures |
| Clozapine withheld for 24 hours, loading dose of phenytoin followed by 300 mg h.s., clozapine restarted at 575 mg/day; maintenance=575 mg/day of clozapine+300 mg/day of phenytoin; three unwitnessed seizures occurred after discharge, but phenytoin blood levels were subtherapeutic; clozapine was decreased to 450 mg/day, need for compliance was reemphasized, and no further seizures occurred |
| Clozapine decreased to 650 mg/day; symptoms completely resolved, and repeat EEG was within normal limits |
| Anticonvulsant changed to primidone, clozapine dose gradually increased after therapeutic anticonvulsant blood levels reached; second seizure 5 weeks later with 275 mg/day of clozapine and 500 mg/day of primidone; clozapine decreased to 250 mg/day, valproic acid added, and primidone gradually decreased; stability achieved with 325 mg/day of clozapine, 4500 mg/day of valproic acid, and 750 mg/day of primidone |

taken approximately 2000 mg of clozapine during the preceding 24 hours as a suicide attempt. The second patient had a seizure after accidentally receiving 350 mg more than her standing dose of 350 mg b.i.d.

Spontaneous seizures during antipsychotic treatment occur relatively infrequently, and the precise mechanism by which neuroleptics induce seizures is unknown (7, 9, 10). In addition to the individual epileptic potential of each drug, the risk factors for seizures include organic pathology, polypharmacy, high doses, and rapid dose increases (7, 9, 10). The cause of the higher seizure incidence with clozapine is unknown, but further study may help to determine the etiology and, in the process, may elucidate the mechanism of seizure induction for all antipsychotics.

The following recommendations stem from our clinical experience and should be considered when prescribing clozapine in doses higher than 600 mg/day. However, there is a lack of consensus among neurologists on the appropriate management of drug-induced seizures.

1. Any increase in the clozapine dose beyond 600 mg/day should be done only if the patient is not improving with lower doses and only after an EEG has been read as normal.
2. If a patient has a seizure while taking clozapine, all possible metabolic causes for the seizure should be ruled out.
3. Discontinuation of clozapine treatment must be seriously considered.
4. If clozapine treatment is to be continued, additional informed consent should be obtained, and the dose should be decreased to preseizure levels or lower.
5. Treatment with anticonvulsants should be initiated, and the doses should be adjusted to achieve therapeutic blood levels. Phenobarbital, phenytoin, or valproic acid can be prescribed, but carbamazepine should not be given, since it has the potential to cause bone marrow suppression. Since clozapine can cause agranulocytosis, it should not be combined with another medication that can adversely affect the bone marrow.
6. After therapeutic anticonvulsant blood levels are reached, the clozapine dose can be gradually increased if clinically indicated.

Despite the ictal phenomena experienced by these patients while taking clozapine, they elected to continue taking it because of their psychiatric improvement. In addition, each continued to improve slowly but gradually without any apparent neurologic sequelae from their myoclonus or seizures.

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# Growth Hormone Response to Growth Hormone-Releasing Hormone in Schizophrenic Patients

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*Ten schizophrenic patients and five normal control subjects were challenged with growth hormone-releasing hormone in a pilot study investigating growth hormone secretion from the pituitary. The results suggest suprapituitary dysfunction in schizophrenia, but replication in a larger study is needed.*

(Am J Psychiatry 1990; 147:1072–1074)

The neuroendocrine strategy for studying mental disorders consists of measuring peripheral hormonal levels and hormone response to pharmacologic probes to infer the neurochemical activity of the CNS that influences the secretory patterns of these hormones (1). Because abnormal dopamine neuronal function is central to the prevailing hypothesis of the etiology of schizophrenia (2), it is of particular interest to study growth hormone (GH) in this disorder, since dopamine acts through hypothalamic growth hormone-releasing hormone (GH-RH) and the suppression of somatostatin to stimulate GH secretion (3, 4). Pathologic involvement of hypothalamic dopamine function in schizophrenia may be reflected in secretory abnormalities of GH (5).

Studies of GH responses to dopamine agonists in schizophrenia have produced variable results. Some have indicated the existence of several types of secretory abnormalities in schizophrenia, including increased variability in basal GH levels and exaggerated or blunted GH responses to pharmacologic stimulation (6). The anatomic locus of GH regulatory dysfunction has not been determined. To evaluate anterior pituitary GH response directly, we administered (for the first time, to our knowledge) the hypothalamic peptide GH-RH to schizophrenic and normal control subjects. Exogenous GH-RH bypasses the hypothalamus and stimulates the pituitary directly, thereby allowing us to determine pituitary function. If the pituitary response is normal in schizophrenic patients, then the aberrant GH secretory responses to dopamine agonists can be assumed to arise from hypothalamic or suprahypothalamic dysfunction in schizophrenia.

## METHOD

The study subjects consisted of a group of 10 patients with schizophrenia (three first-episode patients and seven chronic patients) and a group of five normal control subjects. The patients were selected from two ongoing studies, and the control subjects were obtained through local college and newspaper advertisements. The age and sex distributions were similar in the two groups: the mean age of the patients was 27.9 years (range=23–37), and the mean age of the control subjects was 25.8 years (range=23–32). Three of the patients were female, and two of the control subjects were female.

The patients had diagnoses of schizophrenia or schizoaffective disorder, as defined by *DSM-III*, based on histories and clinical interviews by research psychiatrists. The first-episode patients were interviewed with the Schedule for Affective Disorders and Schizophrenia (7) and had not had previous exposure to neuroleptics. The chronic schizophrenic patients were multiepisode patients who had been resistant to standard neuroleptic treatment and were candidates for treatment with an investigational neuroleptic.

The patients were free of any medical or endocrine disorders, as determined by history and physical examination, CBC, SMA-20, ECG, VDRL, and thyroid function tests. None was receiving supplemental hormonal therapy. They did not use ethanol excessively

Presented in part at the International Congress on Schizophrenia Research, San Diego, April 4, 1989. Received Aug. 30, 1989; revisions received Oct. 17, 1989, and Feb. 7, 1990; accepted Feb. 12, 1990. From the Department of Research, Hillside Hospital; the Department of Quantitative Analysis, St. John's University, Jamaica, N.Y.; and the Department of Medicine, Long Island Jewish Medical Center, New Hyde Park, N.Y. Address reprint requests to Dr. Mayerhoff, Department of Research, Hillside Hospital, 75-59 263rd St., Glen Oaks, NY 11004.

Supported by NIMH Research Scientist Development Award MH-00537 to Dr. Lieberman and grant MH-41960 to the Mental Health Clinical Research Center of Hillside Hospital-Long Island Jewish Medical Center.

Synthetic human growth hormone-releasing hormone was provided by Dr. Michael Thorner. Andrei Balas aided in the sterile preparation of the diluent.

The authors thank John M. Kane, M.D., for his comments on the manuscript and Judy Dunlop, R.N., for conducting the infusion procedures.

(300 ml/week) and were taking no medications that could alter GH secretion (i.e., dopamine agonists). All subjects' weight was generally within the ranges listed as desirable in the Metropolitan Life Insurance Company weight tables. All subjects were within 20% of their ideal body weight, which was an a priori criterion for entry into the study. There were no histories of dramatic weight changes in the 6 months before the subjects participated in the study. No subject was pregnant. All of the subjects gave written informed consent.

All of the normal control volunteers were mentally and physically healthy. They were screened with a clinical interview conducted by a research physician (D.I.M.) and a doctoral-level psychologist. In addition, a trained research assistant completed a Structured Clinical Interview for DSM-III for each of them. All volunteers had baseline evaluations that included medical history, blood chemistries, CBC, and ECG.

The patients had been drug free for a minimum of 14 days before the GH-RH injection and were generally tested within the first 2–4 weeks after admission to the hospital. After an all-night fast, at 9:00 a.m. the patients were brought to a special procedures room. A butterfly cannula was inserted into an antecubital vein and connected by a three-way stopcock to a normal saline infusion with 5 U/ml of heparin to keep the vein patent. The intravenous procedure was started 45 minutes before the injection of GH-RH. All subjects were injected by intravenous bolus with 1 μg/kg of GH-RH. (Lyophilized GH-RH had been reconstituted in bacteriostatic saline that was first brought to a pH of 3 with hydrochloric acid and filtered through a 0.22-μm filter; 1 cc of diluent was added to 100 μg of GH-RH.)

Blood samples were obtained, beginning 30 minutes after catheter insertion, 15 and 0 minutes before the injection and 15, 30, 45, 60, 90, and 120 minutes after the injection. Vital signs (blood pressure, heart rate, and respiration) and subjective side effects were monitored throughout the procedure. Blood samples were collected in heparinized tubes, and plasma was separated by centrifugation and stored at −20 °C to await analysis. The samples were analyzed for GH by double-antibody radioimmunoassay (8), and all samples were tested in the same assay.

## RESULTS

No subjects experienced any adverse effects, even transient ones, from the GH-RH injection. One patient became agitated and refused to continue the procedure 90 minutes after the injection.

GH responses to the injection are shown in table 1. No significant differences between the schizophrenic and control groups were found on any of the variables. There was a trend toward a difference in time to reach the peak GH value, but the difference was not statistically significant ($t=1.93$, $df=13$, $p=0.08$).

A two-way repeated measures analysis of variance was performed on the integrated GH secretion data. The Group (patients versus control subjects) by Time (preinjection versus postinjection) interaction was not significant ($F=0.06$, $df=1, 13$, $p=0.82$), indicating a similar pattern of response to GH-RH over time in both groups. Parametric tests performed on transformations of the data and nonparametric analogs of the data also yielded nonsignificant differences. Similarly, no significant differences were found between the chronic patients and the first-episode patients. A trend toward delayed time to reach the peak GH value in the first-episode patients was not statistically significant. In light of the limited sample size and the high risk of making a type II error, these negative findings must be cautiously interpreted before they are generalized to all schizophrenic patients.

**TABLE 1. Growth Hormone (GH) Responses of 10 Schizophrenic Patients and Five Normal Control Subjects to an Injection of Growth Hormone-Releasing Hormone**

| Variable | Schizophrenic Patients | | Control Subjects | |
|---|---|---|---|---|
| | Mean | SD | Mean | SD |
| Area under GH curve (ng/ml per 15-minute interval) | | | | |
| Before injection | 19.1 | 18.4 | 10.5 | 4.5 |
| After injection | 148.9 | 104.4 | 128.1 | 76.0 |
| Percent increase in area under GH curve | 982.7 | 942.3 | 1761.3 | 2171.2 |
| Peak GH value after injection (ng/ml) | 17.4 | 11.6 | 16.5 | 7.9 |
| Time to reach peak GH value (minutes) | 45.0 | 18.7 | 27.0 | 12.5 |

## DISCUSSION

The GH responses to GH-RH elicited in the control subjects and schizophrenic patients appear to be consistent with those reported in normal subjects in the endocrinologic literature (9). The data suggest that the pituitary somatotropic cells in patients with schizophrenia are capable of normal GH responses when stimulated directly. The results of this pilot study are consistent with the hypothesis that pathology at a level above the pituitary affects GH responses to dopamine agonists in schizophrenia. However, these findings must be viewed as preliminary because of the low statistical power resulting from the small number of subjects. The importance of applying the method used in this study to a larger sample is that any abnormalities found in the GH responses of schizophrenic patients can be better localized in the brain.

Besides confirming these results by the study of larger numbers of subjects, future research in this area should also use selective pharmacologic probes for possible neurotransmitters that regulate GH-RH secretion from the hypothalamus. These measurements of GH should be coupled with GH-RH stimulations of

GH in the same subjects in order to obtain a more complete characterization of neuroendocrine function in schizophrenia (10).

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# Role of Cigarette Use in Hyponatremia in Schizophrenic Patients

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*Urine volume and osmolality were studied in two schizophrenic patients with hyponatremia and six normal subjects after they smoked or ingested cigarettes. The results suggest that cigarette use may contribute to the development of hyponatremia by impairing water excretion.*

(Am J Psychiatry 1990; 147:1075–1077)

Hyponatremia due to water intoxication is a common problem in schizophrenia, occurring in about 3% of patients (1). It may be clinically significant and associated with severe neurologic consequences, including seizures, coma, and even death (2). While compulsive water drinking is clearly an important factor in the production of hyponatremia in these patients, it is likely that a concurrent defect in urinary dilution is present (3, 4). Such an impairment in water excretion has been attributed both to antipsychotic medication (5) and to acute psychosis (6) in these patients.

Use of cigarettes may also play a role in producing hyponatremia in schizophrenic patients. Heavy smoking is highly prevalent in these patients (7), and some even ingest cigarettes. Smoking is known to stimulate secretion of vasopressin and thus cause urinary concentration (8, 9). In the setting of profound polydipsia, the resulting impairment in renal water excretion may result in hyponatremia.

We report the results of clinical investigations of two schizophrenic patients admitted to the hospital with hyponatremic seizures. In both cases, cigarettes were implicated as a factor in the pathogenesis of the hyponatremia. To further evaluate the effect of cigarette smoking on renal water excretion, we measured urine volume and osmolality in normal, water-loaded subjects at baseline and after cigarette smoking.

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## CASE REPORTS

*Case 1.* Ms. A, a 53-year-old schizophrenic woman, was admitted to the hospital because of worsening psychosis. Her serum sodium level at admission was 142 mmol/liter (normal range=136–148 mmol/liter). The patient was started on loxapine for management of her psychosis. It was noted that she drank water excessively and ate cigarette butts from ashtrays. On the sixth hospital day she had a grand mal seizure. At this time her serum sodium level was 112 mmol/liter and her plasma osmolality was 232 mmol/kg (normal range= 275–295 mmol/kg). The concurrent urine osmolality was inappropriately elevated at 364 mmol/kg (normal during water loading, <100 mmol/kg), and her serum creatinine level was 62 μmol/liter (normal range=53–134 μmol/liter). There was no evidence of volume depletion or cardiac, hepatic, or renal disease. The patient's loxapine was discontinued, her fluid intake was restricted, and the hyponatremia disappeared within a few days. Loxapine was restarted, and over the next 6 days Ms. A's sodium level remained normal.

*Case 2.* Mr. B, a 39-year-old schizophrenic man, was brought to the hospital after having had a witnessed grand mal seizure. He was found to have a serum sodium level of 106 mmol/liter. His urine specific gravity was inappropriately high at 1.014. The patient was known to be a compulsive water drinker and heavy smoker. His serum creatinine level was 53 μmol/liter, and the uric acid level was 170 μmol/liter (normal range=155–357 μmol/liter). There was no evidence of volume depletion or cardiac, hepatic, or renal disease. With fluid restriction Mr. B's hyponatremia was corrected within a few days.

## METHOD

In addition to the two schizophrenic patients we have described, six normal subjects with no known medical problems were recruited for the study. There were four men and two women whose ages ranged from 33 to 38 years. All were health professionals who were long-term smokers. Informed consent was obtained for participation in the study protocol, which was approved by the University of Oklahoma Institutional Review Board. The normal subjects and the two patients fasted and refrained from smoking for 12 hours before the study began. At the beginning of the study, each subject received an oral water load consisting of 20 ml/kg of tap water consumed over 20

**TABLE 1. Effect of Cigarette Smoking or Ingestion on Urine Volume and Osmolality During Water Loading in Two Schizophrenic Patients and Six Normal Subjects**

| Measure | Schizophrenic Patients | | | | Normal Subjects | | | |
|---|---|---|---|---|---|---|---|---|
| | Patient 1 | | Patient 2 | | | | Analysis of Difference From Basal Level | |
| | Basal | After Cigarette Ingestion | Basal | After Cigarette Smoking | Mean | SD | t (df=5) | p |
| Urine volume (ml/min) | 12.6 | 2.3 | 16.1 | 5.8 | | | | |
| Basal | — | — | — | — | 11.2 | 1.3 | — | — |
| After cigarette smoking | | | | | | | | |
| 30 minutes | — | — | — | — | 5.9 | 4.5 | 3.72 | <0.01 |
| 60 minutes | — | — | — | — | 1.9 | 1.3 | 16.64 | <0.001 |
| 90 minutes | — | — | — | — | 3.8 | 4.5 | 3.60 | <0.01 |
| 120 minutes | — | — | — | — | 6.8 | 3.3 | 2.31 | <0.05 |
| 150 minutes | — | — | — | — | 8.4 | 2.0 | 2.36 | <0.05 |
| Urine osmolality (mmol/kg) | 53 | 211 | 56 | 133 | | | | |
| Basal | — | — | — | — | 63 | 20 | — | — |
| After cigarette smoking | | | | | | | | |
| 30 minutes | — | — | — | — | 143 | 118 | 1.60 | n.s. |
| 60 minutes | — | — | — | — | 281 | 121 | 4.48 | <0.01 |
| 90 minutes | — | — | — | — | 314 | 165 | 3.28 | <0.05 |
| 120 minutes | — | — | — | — | 161 | 109 | 2.00 | n.s. |
| 150 minutes | — | — | — | — | 71 | 25 | 1.60 | n.s. |

minutes. Serial urine samples were collected every 30 minutes until the subject achieved a steady-state rate of urine flow (two consecutive collections in which the flow rate differed by 10% or less). Following collection of each urine sample, the subject ingested a similar volume of water plus 10 ml to replace imperceptible losses.

At the end of the baseline period, each subject was asked to smoke two cigarettes over a period of 15 minutes and to inhale deeply. Some subjects experienced transient lightheadedness, but none developed nausea. (The schizophrenic patient in case 1, who was a nonsmoker, chewed and swallowed two cigarettes.) Consecutive 30-minute urine samples were collected for 2½ hours after the cigarettes had been used, and water replacement was also continued. Blood samples were obtained in heparinized tubes before the cigarette smoking or ingestion and at the end of the experiment. The subjects remained seated throughout the study except when voiding.

Blood samples were promptly centrifuged and the plasma separated for subsequent assays. Urine and plasma osmolalities were measured by freezing-point depression, and creatinine levels were measured by an automated Beckman analyzer. Free water clearance was calculated from the formula $V(1-U_{osm}/P_{osm})$, where $V$=urine volume, $U_{osm}$=urine osmolality, and $P_{osm}$=plasma osmolality. The glomerular filtration rate of each subject was estimated from the mean of the creatinine (cr) clearances measured in the last two basal urine samples ($U_{cr} \times V/P_{cr}$).

The baseline values of each parameter were determined from the mean of the last two baseline clearance periods. Differences between the baseline and experimental values were compared by analysis of variance for repeated measurements followed by paired t tests. A p value <0.05 was considered statistically significant.

## RESULTS

In the first schizophrenic patient, following ingestion of two cigarettes, the urine flow rate decreased by 82%, while the urine osmolality rose fourfold (table 1), resulting in a 94% reduction in free water clearance, from 10.2 to 0.6 ml/min. In the second patient, smoking two cigarettes decreased the urine volume by 64% and increased the urine osmolality from 56 to 133 mmol/kg, resulting in a 77% reduction of the free water clearance, from 12.9 to 3.0 ml/min.

The acute effect of smoking two cigarettes on renal water excretion in the normal subjects is summarized in table 1. The mean urine volume decreased to 53% of the baseline level within 30 minutes of smoking and reached a nadir of 17% of the baseline level by the end of the first hour. The urine flow rate then gradually recovered to basal values over the next 90 minutes. Urine osmolality doubled within the first 30 minutes, reached a peak that was fivefold higher than the baseline level at 90 minutes, and then returned to basal values in the last hour. The net effect of the changes in urine volume and osmolality was to decrease free water clearance by 94% at 60 minutes after smoking, from a mean±SD of 8.7±1.6 to 0.5±1.1 ml/min ($t=14.5$, $df=5$, $p<0.001$). In four of the subjects, urine osmolality transiently exceeded plasma osmolality, resulting in a net negative free water clearance.

Mean±SD plasma osmolality was 280.3±2.4 mmol/kg in the baseline period and decreased to 276.6±2.4 at the end of the experiment ($t=3.40$, $df=5$, $p<0.01$). The mean creatinine clearance in the

normal subjects was 135±10 ml/min and was unchanged after cigarette smoking.

## DISCUSSION

In both the schizophrenic patients and the normal subjects, smoking (or ingestion) of cigarettes produced a rapid, transient decrease in urine volume and increase in urine osmolality. Because fluid consumption was limited to compensate for urinary losses during the experimental period, none of the subjects developed significant hyponatremia. If water intake had been increased, however, the resulting positive water balance would no doubt have produced a progressive drop in plasma osmolality.

Both of the schizophrenic patients were noted to have inappropriately concentrated urine when their hyponatremia was detected. In Ms. A the drug loxapine was initially thought to have produced a syndrome of inappropriate secretion of antidiuretic hormone. This hypothesis was apparently supported by the onset of hyponatremia within a few days of starting loxapine and resolution of the hyponatremia after discontinuation of the drug. However, since the patient appropriately diluted her urine in response to the water load after loxapine had been restarted, the drug was probably not responsible for her developing hyponatremia. The changes in urine volume and osmolality after the smoking or ingestion of cigarettes in the two schizophrenic patients strongly suggest a role for the cigarettes in producing the hyponatremia.

A previous report has also implicated smoking as contributing to the hyponatremia observed in schizophrenic patients (10). The patient developed significant hyponatremia during a period of unrestricted smoking and water consumption. Moreover, cigarette use is a common characteristic of schizophrenic patients with chronic hyponatremia (7) and may contribute to the pathogenesis of this electrolyte disorder (3).

Because of the rapid reversibility of the effect of cigarettes on renal water excretion, their role in producing hyponatremia may frequently be overlooked. Following a hyponatremic seizure, the patient stops smoking, and the effect on vasopressin rapidly wears off. Delayed measurement of the urine osmolality will yield an appropriately low value, masking the prior elevation.

The observations in this study suggest that cigarette smoking (or ingestion) may be a frequently overlooked factor contributing to the pathogenesis of hyponatremia in schizophrenic patients. An increase in water intake in combination with impaired renal water excretion induced by cigarette use may be sufficient to produce symptomatic hyponatremia in these patients.

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# Book Forum

## Nancy C. Andreasen, M.D., Ph.D., Editor

SCHIZOPHRENIA

**Treatment of Schizophrenia: Family Assessment and Intervention,** *edited by Michael H. Goldstein, Iver Hand, and Kurt Hahlweg. New York, Springer-Verlag New York, 1986, 215 pp., $34.50.*

This excellent, rather slim volume deals with schizophrenic patients and their families. It contains contributions by the leading international experts in family studies and is the updated product of two workshops sponsored by the University of California, Los Angeles, Department of Psychology and the Max Planck Institute of Psychiatry in Munich.

The role of the families of schizophrenic patients has become an emotionally laden subject. We have come full circle from a time when psychiatrists blamed families for the development of schizophrenia to the point where families now criticize psychiatry for implying that families have anything to do with the etiology, course, or outcome of the illness. As Goldstein states in the preface, "Many relatives of schizophrenic patients experienced some form of rebuff by the mental health professionals while their relative was treated as a patient and little or no involvement in the aftercare process when their relative returned home." Today, treatment of schizophrenic patients would not be considered adequate if family members were not involved in the therapeutic program.

*Treatment of Schizophrenia* is divided into two sections: Predictors of the Course of Schizophrenia and Modification of the Course by Family Interventions. In addition, there is an interesting epilogue by Liberman. In the section on prediction of the course of schizophrenia, the major focus is on the Camberwell Family Interview and the measurement of expressed emotion. Hooley states that expressed emotion is currently one of the most important measures of family functioning available to clinicians and researchers working with schizophrenic patients. Family levels of expressed emotion are assessed by means of the Camberwell Family Interview, a nonschedule standardized interview that takes between 1 and 2 hours to administer.

The interview is conducted with the patient's closest relative and is audiotaped for later coding. Five different ratings are made: 1) Criticism: the sum total of critical remarks the relative makes about the patient in the course of the interview. 2) Hostility: unlike criticism, which is situation-specific, hostility involves a greater generalization of negative feeling and usually includes remarks critical of the patient rather than of the patient's actions or behaviors (e.g., "He is stupid"; "Everything she does is stupid"). 3) Emotional overinvolvement: a dramatic or exaggerated emotional response to the patient's illness. 4) Warmth: based on the voice tone of the speaker. 5) Positive remarks: defined primarily by content, these reflect unambiguous praise or appreciation for some characteristic or behavior of the patient. The last two measures are not often referred to in the literature, probably because they have been found to add little to the predictive power of expressed emotion ratings.

Studies have shown that when families are divided into those with high or low expressed emotion on the basis of an interview during the patient's hospitalization, patients from families with low expressed emotion are less likely to relapse after hospital discharge. There are many important questions regarding the concept of expressed emotion. What is it essentially? Is it nothing more than a measure of an easily detectable stress that family members place on vulnerable schizophrenic patients? Hooley states that relatives with high levels of expressed emotion are not easy to spot and that a long training period in conducting the Camberwell Family Interview is needed in order to achieve good reliability. However, Buchkramer et al. describe a simple measurement instrument, the Munster Family Interview, and Wynne and others have used the Five Minute Speech Sample technique, which counts critical comments. Both of these instruments have been shown to be good predictors of relapse. In the chapter by Vaughn, there is a statement that all clinicians should remember: "There was no suggestion that the family qualities or characteristics to be identified by the Camberwell Family Interview were necessarily deviant or that they were unique to the relatives of schizophrenic patients."

This book deals with many other critical issues regarding families and the outcome of patients: Does expressed emotion in a family change spontaneously over time as the patient's condition changes? Can family education and treatment convert a family with high expressed emotion to low expressed emotion? Is there any relationship between a patient's behavior and family levels of expressed emotion? Do measures of attitudes and feelings obtained during the Camberwell Family Interview correlate with actual family behavior in the home situation? Does low expressed emotion mean only that the family expresses little negative feeling, or are there other characteristics of such families? Are there differences in patients' psychophysiological measures when they are in the company of family members with high or low expressed emotion? How does one explain the results of a study described in this book which found that expressed emotion was not predictive of relapse? Is the measure of expressed emotion useful in predicting the course of depressive disorders?

The discussions and descriptions of studies that deal with these questions are of a uniformly high quality and very illuminating for both researchers and clinicians dealing with schizophrenic patients and their families. *Treatment of Schizophrenia* is a compact volume, well worth reading and studying.

MARVIN I. HERZ, M.D.
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**Schizophrenia: An Integrated Approach to Research and Treatment,** *by M.J. Birchwood, S.E. Hallett, and M.C. Preston. New York, New York University Press, 1989, 403 pp., $42.00.*

One could reasonably ask why yet another book on schizophrenia has been published. This book is an answer to that question. Although there is a sea of material promising an integration of information on schizophrenia, this is one book that delivers the promised synthesis. It is divided into five large sections: Conceptual Issues, Biology, Environment, Treatment, and the final Integration of Information. All the chapters are concise and factually correct.

The authors begin with an explanation of the concept of schizophrenia as an illness. The ideas of Bleuler and Kraepelin are well represented, and descriptions of actual cases are well done. The authors succeed in producing as good a definition of schizophrenia as I have seen anywhere. They present an interesting section on the cross-cultural acceptance of the quality of delusions. The cross-cultural approach is a good way to convey the importance of consistency in defining what are really the critical diagnostic features of schizophrenia. It also adds to the construct validity for the concept of schizophrenia.

The part of the book that deals with biological issues is uneven. It begins with an excellent review of genetic information on schizophrenia. The material on genetics is entirely correct and adheres to good epidemiologic techniques in its method. Family studies and adoption studies are properly discussed. The presentations of biochemical theories and neuroanatomy, however, require more detail than is provided. The discussion of regional brain function and EEG is really too brief. The chapter on cognitive functioning is reasonably detailed, informative, and well organized. The presentation of findings from high-risk studies is adequate. Although it was a good idea to make high-risk research a separate chapter, the area could have been better developed and would have stood alone had it been more detailed.

The authors' presentation of environmental effects is quite good. The synthesis of data concerning the interaction of genetic and environmental effects is excellent. The skillful integration of many studies lends support to the "stress-diathesis" model for schizophrenia. The discussion of social outcome is good but does not yield a great deal of new information. There is also an interesting look at theoretical origins for auditory hallucinations.

Part four is a very interesting overview of treatment modalities. So much is written about somatic treatment these days that it is refreshing to see a good synopsis of nonmedical forms of intervention. Topics ranging from operant conditioning to social interaction are well represented. The use of token economy is briefly reviewed. Pharmacological treatments are presented in a brief but accurate synopsis. Although the authors are psychologists, their discussion of treatment is well balanced between somatic and nonmedical approaches. The material is factually presented and does not suggest parochial stratification between psychologists and medical practitioners. Furthermore, there is no indication that the discussion is biased against psychiatrists or in favor of a particular treatment. On the whole, it is very objective.

It is good to see a book that deals with rehabilitation. This topic is too often overlooked in other texts. Rehabilitation leads naturally to the integration of the previous subject matter of the book. The chapter on rehabilitation goes beyond the treatment of acute situations and focuses on the ongoing needs of the schizophrenic individual. The authors deal with this topic logically and effectively, without losing the human quality necessary to deal with sick people.

*Schizophrenia: An Integrated Approach to Research and Treatment* is a refreshing look at important issues in schizophrenia. It deals with many concepts and manages to synthesize them into an interesting and informative book that would be a good contribution to the library of both clinicians and researchers. It makes good use of both clinical vignettes and research studies, adapting them to the needs of the reader interested in schizophrenia. The book would be a good text for the undergraduate as well as the experienced practitioner.

JAMES ALLEN WILCOX, D.O.
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**Treating Schizophrenia,** *by Werner M. Mendel. San Francisco, Jossey-Bass, 1989, 233 pp., $24.95.*

This book comes at the end of the decade that produced more information about schizophrenia than any before it. From symposia to journal articles to multiauthored monographs and textbooks, the explosion of descriptive data comes tumbling forward. Newly trained psychiatrists are in little better position than experienced ones to know what to filter out as clinically most relevant.

Consider taking a breather from the scientific avalanche by spending a few hours with this book, which is not wholly unscientific. From several thousand patients with whom he has had contact from the 1950s through the 1980s, Dr. Mendel presents information on 497 followed longitudinally. Although the methods of his study (such as inclusion and exclusion criteria and specific length of follow-up) are not stated, many characteristics of the patients are known. Doubtless this group of patients differs from many groups of inner city clinic patients: 20 never received psychotropics, only two developed tardive dyskinesia, only three committed suicide in 35 years, and the group as a whole demonstrated normal life expectancy and reproductive rates. Sixty-three percent were seen privately and 37% in the public sector. Dr. Mendel's diagnostic perspective is distinctly Bleulerian, and I wonder whether his good outcomes are due solely to the careful, individualized, "first do no harm" approach to treatment he eloquently describes.

The first several chapters of the book are grouped together as Part One: The Disease. They are concerned with natural history—age at onset, periodicity of exacerbation and remission, prognosis, subtypes, and the effects of treatment on the course of the illness. Dr. Mendel challenges the notion that the course of schizophrenia is relentlessly downhill and argues that successful community reintegration of patients is the primary force in avoiding debilitation. The issue of diagnosis and diagnostic subtypes is not fully addressed until chapter seven, rather late for a presentation of this kind. However, his discussion of the phenomenon of exacerbation and remission, with the interplay of host, disease, and environment, is that of a wise and experienced clinician.

The remaining chapters are grouped as Part Two: The Treatment and are more personal. Here the author presents his views about what works and what does not, what treatments are used frequently even though they do more harm than good, what elements of the physician-patient relationship are particularly potent when dealing with schizophrenic

patients, and how to provide supportive care while at the same time avoiding the pitfalls of dependence. Chapters 11–13 are the strongest; they are concerned with supportive care, hospitalization as acute intervention, and the psychology of prescribing medication. Less clear are Dr. Mendel's techniques for increasing community acceptance of schizophrenic individuals and managing the amotivational state many schizophrenic patients develop, two major problems in any outpatient treatment or rehabilitation program. Although Dr. Mendel's chapter on the psychology of medication is masterful, the one on guidelines for the use of medications, by Patricia J. Lobeda, Pharm.D., is brief, oversimplified, and of little use as a reference. Its presence detracts from the rest of the book.

Since *Treating Schizophrenia* is a relatively brief synthesis of what is known about the clinical management of schizophrenia, theoretical topics such as etiology and neurobiology are omitted. The bibliography contains about 170 references, current through 1988. The index is excellent.

The cases of two patients are presented in detail. Mendel asks the reader to "be a phenomenologist . . . . Discover their disabilities and their defects but also their strengths and their humanity. See how they are like you and yet how they are different." This sensitivity, however, does not lead him to claim that the illness is curable through psychotherapy or that it should be approached with anything other than a fair dose of clinical common sense. With the perspective of a clinician who has seen treatments and theories come and go, Dr. Mendel tries to bring us back to the basics of treating a condition that is at once ultimately mysterious, responsive to intervention, and rewarding to treat. On balance, concerns about the methods of this "study" are lessened by the weight of the author's experience. *Treating Schizophrenia* is a timely and satisfying book.

SCOTT MCCORMICK, M.D.
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**A Clinical Guide for the Treatment of Schizophrenia,** *edited by Alan S. Bellack. New York, Plenum, 1989, 329 pp., $39.50.*

This is an up-to-date, generally useful, and informative text about many aspects of optimal treatment of schizophrenic patients in the late 1980s. Since it is multiauthored, some chapters, as may be expected, are better than others. The editor contributes an opening chapter describing the need for a comprehensive model of treatment and then unobtrusively permits each succeeding chapter to speak for itself. I would have preferred an explanation as to why particular topic areas or specific authors or investigators were selected, and I would have welcomed a concluding chapter to weave the whole book together. At the end I felt, as schizophrenic patients and their families must feel, that a panoply of interesting treatments are out there and available but that no one has taken the trouble to steer me through them. I felt like a patient managed by a "case manager" as if I were a case, leaving individual needs unmet.

There are two chapters on psychopharmacology. The second, by John Kane, contributes new knowledge about nonresponse to and noncompliance with neuroleptics. The important point, raised in Dr. Bellack's opening chapter, that optimum psychopharmacological treatment requires careful and knowledgeable monitoring—a luxury not available to most patients—should have been further addressed. Effectiveness of maintenance strategies depends on skilled and caring physicians who know the patient in depth and over time and whom the patient trusts sufficiently to unveil some of his or her troubling thoughts.

The chapters on community residential treatment and partial hospitalization address important aspects of site, context, and costs of care but bypass the more important issues of what constitutes an effective component of treatment.

The chapter on crisis intervention by Gilbert Weisman is interesting in that it draws on a different theoretical model than the rehabilitation model usually invoked for treatment of chronic conditions. Both models, although inherently antithetical, offer a workable theory on which to base comprehensive services for schizophrenic patients.

The chapters on social skills training and social problem solving address the treatment of specific schizophrenic deficits. In that sense they can be seen as analogous to drug treatments, which also target specific symptoms. Treatment evaluation assumptions are totally different, however. The efficacy of drugs is judged by their ability to keep symptoms at bay as long as the drugs are taken. It would not occur to schizophrenia researchers to give drug and placebo, stop both, and then look for differential effects 6 months later. When it comes to studying the effects of terminated social programs, however, investigators are disappointed when beneficial effects are not apparent at follow-up. Clinical experience shows that deficits in schizophrenia endure and that specific interventions, in order to be effective, need to continue. One cannot assume that reinforcement and continued learning will take place in an unstructured setting. As Dr. Bellack notes in his introductory chapter, the infectious disease model of schizophrenia treatment is not applicable, whether one speaks of chemotherapy, social therapy, or psychotherapy.

The psychotherapy chapter by Dingman and McGlashan is superb. These authors describe the establishment of a relationship and the strategies the therapist uses. They speak of the administrative and triage functions of the therapist and the way the relationship is used for mutative purposes. The contents of this chapter and the chapter on case management by McGill and Surber are not dissimilar. The vocabulary of each is different, but, in the end, both agree that a stable, continuous relationship with an experienced, committed helper is central to any expectation of change for the patient with schizophrenia.

The patient's family is not forgotten, since the family is usually the primary agent of change. There are two chapters devoted to families: "Family Education" and "Behavioural Family Therapy." The first notes the potential pitfalls as well as possible advantages of psychoeducation. The second gives many examples illustrating the technique of behavioral family therapy.

This book provides the reader with theoretical structure, practical guidance, and excellent references. It is a valuable treatment guide, although the connections among treatments are not explored and each one seems to be a compartment all its own rather than what the editor intended, an imbedded part of a comprehensive whole.

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## MOOD DISORDERS

**New Directions in Affective Disorders,** *edited by Bernard Lerer and Samuel Gershon. New York, Springer-Verlag New York, 1989, 709 pp., $150.00.*

This is an interesting volume to review because it is composed of a large number of very small chapters. Many of the papers in this multiauthored volume were presented at a meeting in Jerusalem in 1987. Additional papers have been added. There are five major sections: Pathogenesis of Affective Disorders and Basic Mechanisms of Drug Action, Neurobiology of Affective Disorders, Affective Disorders in Populations at Risk, Related Affective Syndromes, and New Directions in Treatment. In all there are 149 chapters in just over 700 pages of text. Thus, most of the chapters are quite brief. The referencing for each chapter is quite variable—from sparse to more than 40 references. For the most part, the chapters are authored by knowledgeable experts in the fields they write about. The references extend through 1987 and thus are reasonably current for a volume of this type.

*New Directions in Affective Disorders* is a useful reference text for researchers, and most of the chapters are quite well written. I think that the book might be overwhelming for clinicians but could be of use to residents or postgraduate fellows who are interested in learning the breadth of research in this area. The volume presents a comprehensive overview of research in affective disorders. Although no one topic is covered in great depth, there is sufficient information in each of the short chapters that one can easily grasp the major research data and conclusions.

DAVID L. DUNNER, M.D.
*Seattle, Wash.*

**Cognitive Processes in Depression,** *edited by Lauren B. Alloy. New York, Guilford Press, 1988, 388 pp., $40.00.*

This detailed volume focuses on the subtype of affective disorder known as negative cognitive depression, which derives from Aaron Beck's negative triad—negative expectations concerning the self, the world, and the future. The 12 chapters span a wide range of topics. Chapter one deals with theoretical issues such as clarification and revision of the hopelessness theory of depression. Chapter two discusses research design issues such as the relationship between negative cognitive depression and other subtypes of depression. Chapter three deals with the role of personal stressful life events, focusing on the occurrence of a life event versus its personal meaning as predictors of depression. Chapter four discusses the conceptual distinction between affective and anxiolytic disorders, comparing how patients meeting *DSM-III* criteria for anxiety disorders and those meeting *DSM-III* criteria for affective disorders process information about the self and others. Chapter five focuses on issues of self-management and strategies for coping with unfavorable environmental consequences, such as negative cognitive depression. Chapter six discusses depression, vulnerability, and world assumptions, describing the tendency of depressed patients to view themselves and the world as more evil, less controllable, or more subject to random occurrences than do nondepressed patients. Chapter seven, on the role of self-directed attention, talks about the large discrepancy between real-self and ideal-self ratings and the concomitant narrowing of this gap as patients recover from depression. Chapter eight discusses depressive inference; for example, the perceptions and inferences made by depressed patients have been found to be more accurate than those of nondepressed patients. Chapter nine debates whether the causal attributions of depressed patients are self-serving. Chapter 10 describes the self-worth contingency model of depression, which theorizes a relationship among 1) types of individuals (nonvulnerable-nondepressed, vulnerable-nondepressed, vulnerable-mildly depressed, or vulnerable-clinically depressed), 2) self-schema contents (positive, negative, or both), and 3) self-schema consolidation efforts (strong, well-integrated, positive view of self versus weak, poorly integrated, somewhat fragile positive view of self). Chapter 11 presents an imaginative focus on developmental aspects of affect regulation in depressed and nondepressed children; the evidence suggests that by age 6 the cognitive patterns observed in depressed children are similar to those found in depressed adults. Finally, chapter 12 discusses research evaluating cognitive therapy as a treatment modality for depressive disorders, comparing the effects of cognitive therapy relative to pharmacotherapy and the effects of cognitive therapy combined with pharmacotherapy on the treatment of clinical depression.

One of the most important remaining tasks seems to be to establish the reliability of the negative cognitive depression diagnosis itself first and then to examine systematically the extent to which this nosological subcategory is generalizable to and clearly distinct from other classifications of depression. Is it true, as Seligman (1) conjectured, that negative cognitive depression "may not map directly in a one-to-one fashion onto any existing nosological category of depression"? When one reads the vast psychological literature on negative cognitive depression, it is somewhat disconcerting to wonder how depressed patients diagnosed by more standard criteria might compare with those depicted as having negative cognitive depression.

Alloy's volume should serve a rather wide audience: advanced undergraduates, doctoral candidates, clinicians, research investigators, educators, and biostatisticians. Since clinical depression is one of the most common, serious, and costly of society's mental health problems, the volume should also be valuable to the educated layman with a special interest in mental health issues.

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DOMENIC V. CICCHETTI, PH.D.
*West Haven, Conn.*

**Seasonal Affective Disorders and Phototherapy,** *edited by Norman E. Rosenthal and Mary C. Blehar. New York, Guilford Press, 1989, 386 pp., $45.00.*

Fiction, poetry, music, and paintings are no strangers to the seasonal variations in human moods. It is also no surprise to people living in Northern latitudes, such as the Scandinavians, that entire nations become energetic and happy during long summer days and withdrawn, lethargic, and moody during the long winter nights. Psychiatrists, however, have only recently begun to interpret these variations as potentially relevant clinical phenomena, resulting in a recent spate

of research and writing about the association of mood and affect with duration of daylight. Does the duration of daylight, however, correlate with true diagnosable affective disorder?

This volume, edited by two leading researchers in the field of seasonal affective disorder, is an encyclopedic presentation of information arguing for the validity of the concept of seasonal affective disorder. Organized in four sections, it deals with clinical aspects of seasonal affective disorder, animal research models, pathological correlation between seasons and mood, and phototherapy of winter seasonal affective disorder.

Within each of these sections are chapters written by various authors presenting reviews and up-to-date research material. For the beginner, there is a beautifully written historical overview of seasonal affective disorder. The authors point out that many of the great historical figures in psychiatry noted the relationship between seasons, duration of light, and the moods of human beings. Subsequent chapters present data on seasonal affective disorder in Alaska and seasonal affective disorder in childhood and adolescence. Each supports the existence of seasonal affective disorder but cautions that its diagnosis and definition need to be more firmly elucidated. In the Alaska population, there may be subgroups with underlying neuroendocrine disorder. Seasonal affective disorder is quite unusual in childhood and adolescence. There may also be a reversal of the usual seasonal affective disorder pattern, with depression occurring in the summer.

The second section of this book consists of four chapters reviewing the effect of the seasons on physiological functioning in animals. Hibernation, seasonal changes in body weight, and annual cycles in animals are all discussed in detail as supporting evidence for the likelihood of a seasonal cycling pattern in the human species as well.

Three chapters make up the third section of the book, which focuses on normal human seasonal changes in mood, cognitive performance, sleep, feeding and metabolic functions, thermoregulation, cardiovascular function, and neuroendocrine function as well as the effect of seasons on dopamine functioning. The effect of light in normal volunteers is beautifully presented. Together these three chapters extend the animal studies and convincingly support the proposition that humans, like animals, are subject to a wide variety of cyclic changes that correlate with season and duration and intensity of light.

The fourth and final section of this excellent volume presents six chapters reviewing old data as well as providing considerable new information on phototherapy for winter seasonal affective disorder. Regardless of one's own therapeutic experience or clinical bias, the information presented in these last chapters represents a comprehensive and comprehensible review of the rapidly emerging field of psychiatric phototherapy.

In all, this timely and wonderfully written book has much to offer many different readers. For the researcher and scientist, there are up-to-date reviews of past studies as well as presentations of more recent information. For the clinician, there are excellent chapters supporting the validity of the diagnostic concept of seasonal affective disorder as well as demonstrating the effectiveness of phototherapy. Not every chapter is for every reader, but overall this would be a welcome edition to any psychiatric library.

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**Strategies for Studying Suicide and Suicidal Behavior,** *edited by Irma S. Lann, Eve K. Moscicki, and Ronald Maris. New York, Guilford Press, 1989, 164 pp., $17.50.*

The study of suicide and suicidal behavior is fraught with challenge. Suicide can best be understood through a biopsychosocial synthesis. Unfortunately, few such analyses exist. Thus, the investigation of suicide and suicidal behavior is reflected in studies of epidemiology, biochemistry, behavior, psychodynamics, cultural factors, or family dynamics.

The papers in this book are from an NIMH workshop of the same title. They are grouped into two broad categories of Completed Suicides and Suicidal Behavior. Each chapter offers a thorough review of the literature, describes strengths and weaknesses of the approach to the study of suicide covered in the chapter, and suggests new or promising future approaches. This format and the varied content are invaluable to researchers and students of self-destructive behavior and could improve the quality of future research.

In chapter one, O'Carroll reviews the validity and reliability of suicide mortality data, which could be improved substantially if standard criteria were used in the determination of suicidal death. The second chapter, by Gould et al, explores the concept of cluster suicides and the many unanswered questions about the processes and mechanisms involved in such outbreaks. The next two chapters deal with autopsy data. Stanley and Stanley review biochemical studies that seem to point to major dysfunction of the serotonergic system in the brains of suicide victims. Methodological considerations in the use of the psychological autopsy in the study of adolescent suicides are presented by Brent. This is an excellent critique suggesting that the use of the psychological autopsy in conjunction with biochemical studies could further our biopsychosocial understanding of suicide. The next three chapters deal with suicidal hospitalized patients. Pfeffer offers an incisive critique of studies of suicidal preadolescent and adolescent inpatients. She faults such studies for failing to define or measure the severity of suicidal behavior and not using standardized methodologies or control groups. The Iowa Record Linkage Experience described by Black is a novel and powerful way to identify suicidal risk factors from existing data sources. Another record linkage investigation using emergency room data in the study of adolescent suicidal behavior is presented by Deykin. Multiple problems, including the need for complex strategies to protect confidentiality, may inhibit widespread use of these methods.

The final four chapters discuss community-based studies. Earls, discussing suicidal ideation in primary care settings, makes the point that less than a quarter of youths with persistent suicidal thoughts or multiple attempts are identified in medical records. The problems of identifying suicide-prone youngsters is thoughtfully explored by Rotheram-Borus, who presents a useful flow chart of a triage process. Her suggestion that determining the predictive value of suicidal screening procedures could be done only by following a large cohort of patients and not intervening with those in crises raises serious and unacceptable ethical issues. Suicide surveys in schools are reviewed by Garrison. Moscicki presents a broad overview of the value of epidemiologic studies. Both present valuable data for those interested in epidemiology.

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## ANXIETY DISORDERS

**Anxiety and Its Disorders: The Nature and Treatment of Anxiety and Panic,** *by David H. Barlow. New York, Guilford Press, 1988, 692 pp., $50.00.*

Panic disorder made a good deal of news during the 1980s. Its initial appearance in *DSM-III* was soon followed by the recognition of an effective drug treatment, imipramine. At the same time, a useful behavioral intervention, exposure in vivo, gained increasing acceptance for patients with the complication of agoraphobia. Next, epidemiologic surveys showed that panic disorder, with and without agoraphobia, is among the most common psychiatric disorders. Then, another efficacious drug, alprazolam, became available and the research associated with its development and marketing served to focus worldwide attention on the disorder. As a result of this attention, great numbers of patients with panic disorders were appropriately diagnosed and treated for the first time. As the decade comes to a close, however, there continues to be debate over the validity of this diagnosis. Controversy also exists over the relative efficacy of drug and behavioral treatments. These debates concern the nature, even the existence, of the illness in question.

The central focus of *Anxiety and Its Disorders* is on panic, although it covers the range of anxiety-related disturbances defined in *DSM-III-R*. Consequently, the book reflects the excitement of recent discoveries and the challenge of unresolved issues. David Barlow and his colleagues have been major contributors to our understanding of panic. For example, they developed a standardized interview for use with patients with anxiety disorders. Dr. Barlow and his associates focused attention on the functional relationships between coexisting disorders and were instrumental in getting hierarchical rules eliminated from the *DSM-III-R* classification of anxiety disorders. Recently, Dr. Barlow and his associates developed and tested a psychological treatment for panic that they claim eliminates attacks in most patients. In *Anxiety and Its Disorders* Dr. Barlow puts forward an etiological model for panic disorder that integrates biological and psychological mechanisms and emphasizes interoceptive cues in the generation of spontaneous panic.

For his formulations, Dr. Barlow draws upon the works of such early theorists as Darwin, Cannon, and James as well as later investigators such as Eysenck, Spielberger, and Cloninger. In fact, throughout the book he is careful to cite early work and thinking on his subject. Not only is he scholarly in his approach but he also shows an ability to pull information from a variety of domains together and resolve differing viewpoints. He deals with his topic in considerable depth and, although he comes to definite conclusions, he is clear about where he feels the limits of current knowledge are. The book emphasizes the author's own work yet is comprehensive. It shows his enthusiasm for a subject that continues to stimulate much interest and therapeutic optimism. If he sometimes makes dramatic assertions it is perhaps his way of communicating his feeling for this area of research.

This outstanding volume contains much that is of value for researchers but also includes useful material for clinicians, especially in the second half of the book, which deals with individual disorders. It will appeal to psychologists as well as psychiatrists because it is comprehensive and interdisciplinary in its treatment recommendations. Unfortunately, although research involving drug treatments is discussed in detail, Dr. Barlow views these therapies as relatively ineffective or risky and, in most instances, recommends that they be used as adjuncts to psychological treatments. In this respect his approach does not seem balanced. Of course, to be fair about this, there are relatively few studies comparing drug and behavioral treatments directly. When these become available we will gain a much better understanding of their relative worth and how they should be administered.

This book brings together the work and thinking of a decade in which new anxiety disorders were defined and new treatments developed. The new decade promises to be one of grappling with important unanswered questions and consolidating gains in understanding through refinement of methods and filling gaps in our knowledge. Certainly Dr. Barlow is leading the way with a book containing fresh ideas and a critical examination of the field.

RUSSELL NOYES, JR., M.D.
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**Anxiety: New Findings for the Clinician,** *edited by Peter P. Roy-Byrne, M.D. Washington, D.C., American Psychiatric Press, 1989, 204 pp., $19.95.*

One of the more startling revelations of the Epidemiologic Catchment Area study is the finding that anxiety disorders are our most prevalent psychiatric diagnoses, occurring in 9% of the population over a 6-month period. Why this profile is not reflected clinically in psychiatric practice is a matter for conjecture, but current belief holds that most of these individuals seek and receive treatment in primary care medical settings. This monograph, the fifth in the Clinical Practice series, which evolved from symposia presented at the annual meetings of the American Psychiatric Association, focuses on the issue of somatic symptoms in anxiety disorders—how they relate to etiology and how they affect diagnosis and treatment. The editor of the book is a preeminent researcher and clinician in the area, and most of the contributors are drawn from his colleagues at the University of Washington in Seattle. The first three chapters focus on the interaction between panic disorder and cardiac symptoms, hyperventilation, and irritable bowel syndrome. The authors succinctly and impressively provide a history of the literature on phenomenology, review causation theoretically and critically, and provide original data. Bibliographies are extensive and up-to-date.

Succeeding chapters explore the anxiogenic effects and precipitants of caffeine and ethanol use and, with some overlap with an earlier chapter, the issue of anxiety-related cardiovascular risk factors. Finally, reviews of psychopharmacological and biobehavioral treatment strategies are presented. The discussion of drug management is one of the most succinct and sensible essays on the topic currently available. The overview of behavioral interventions is less successful, peculiarly inflated by overly simplified speculations on the roles of ACTH and opioid compounds in the acquisition and extinction of avoidance responses and an unnecessary emphasis of the writer's firsthand experience, an issue that arises earlier in a chapter by another author on treating anxiety syndromes in alcoholics.

Although undoubtedly mandated by the Clinical Practice series format, the recurrent inclusion of one-paragraph clinical vignettes is awkward, its presence perhaps based on the somewhat cynical supposition that the clinician will not find the issues reviewed reflective enough of "real life" practice or, worse yet, will not purchase the volume unless each topic

is preceded by a short listing of the complaints of Mr. D., a 35-year-old lawyer, or K.C., a 23-year-old single female hairdresser, among others. The practice, not limited to this series, pays homage to a human love of fable and myth but emerges, in academic works, at the cost of a more comprehensive discussion of substantive issues. Controversies involved in the U.S. and European classifications of anxiety disorders, the utility of the distinction between spontaneous and situational panic attacks, and the relationship between such factors as caffeine and nicotine or benzodiazepines and alcohol are perhaps the cost of "case illustrations." The title is punchy, but there are no specific chapters on obsessive-compulsive disorder, posttraumatic stress disorder, or anxiety syndromes in children.

Overall, however, this is a scholarly and well-edited book that is as reflective of current knowledge and practice as can be attained in a hardcover work. It is an advisable purchase, not only as a "how to" book but also as an informed theoretical integration of the ways in which behavioral symptoms of anxiety, autonomic arousal, and social learning may interact to produce psychiatric pathology.

VICTOR I. REUS, M.D.
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**Panic and Phobias: Empirical Evidence of Models and Long-term Effects of Behavioral Treatments,** *edited by Iver Hand and Hans-Ulrich Wittchen. New York, Springer-Verlag New York, 1986, 127 pp., $38.50.*

If you have a phobia about prescribing medication to patients with panic attacks, agoraphobia, or anxiety disorders, and if you worry that biological models of panic disorder are overrated at the expense of behavioral cognitive approaches, you may derive some solace from this book. The foreword by Isaac Marks and the introduction by Hand and Wittchen contain stirring statements that stop just short of exclaiming, "Behaviorist, aux barricades, we shall never surrender." If you share this perspective, the battle cry will renew your courage. If you do not, you will find this book irritating or a regrettable purchase.

"Human emotion seems to have changed since *DSM-III* burst on the world in 1980 . . . . With alacrity panic disorder has been clutched to the psychiatric bosom as proof of our medical identity . . . . Alas, we have been there before," writes Marks in the foreword. He adds, "Spontaneous panic is almost as frequent in anxious depression as in panic disorder . . . . The response to lactate infusions or $CO_2$ inhalation by cases of panic disorder is not a specific biological marker, the higher levels of anxiety and arousal that are attained during such challenges largely being a function of their higher baseline level compared with that in controls." These are but two statements by Marks to raise some eyebrows. In the introduction that follows, Hand and Wittchen make their displeasure with the "biological panic concept" clear by asking, "Were panic researchers not familiar enough with the behavior therapy literature?"

The book, organized in three sections, is derived from three symposia on anxiety disorders during the 15th Congress on Behavior Therapy. Section one is devoted to diagnostic reliability and epidemiology. Wittchen and Semler's chapter on diagnostic reliability is useful, valuable, and well written. The central point is that interrater reliability is best achieved with structured standardized interviews, which are superior to clinical checklist assessments. I wholeheartedly agree. Wittchen's chapter on the epidemiology of panic attacks and panic disorder contains interesting data. In addition, he makes an attempt to test the "symptom progression model," which suggests that panic attacks play a key etiological role in the development of agoraphobia. Reporting that "almost 50% of patients with agoraphobia have never experienced either a panic-like state or the full picture of a panic disorder," Wittchen concludes that his data "underline the importance of retaining agoraphobia as a distinct diagnostic category." I differ with this interpretation.

Over the past decade, I have said that I do not think that panic attacks per se are the only or even the central or key driving force in panic disorder or agoraphobia. Rather, limited symptom attacks appear to play a more central and essential role than panic attacks and are the lowest clinical common denominator in both disorders. I predict that the current categories of panic disorder and agoraphobia will turn out in the long run to be severe forms of a genetically inherited biological disorder characterized by limited symptom attacks. I call this disorder endogenous anxiety; it is larger than and encompasses the two existing categories of panic disorder and agoraphobia. Only when we have adequate laboratory tests to probe these disorders will we know with greater confidence. In the meantime, nothing in Wittchen's data is inconsistent with this position.

The five chapters in section two review current theoretical models for panic attacks and the empirical evidence for these models. These chapters are valuable, although they are introduced with a behaviorist's bias. Hand and Wittchen introduce this section by stating that Van den Hout and Griez, in their chapter "Biobehavioral Notes on Empirical Findings," found no "convincing evidence for the view that panic is caused by underlying pathophysiological abnormalities in acid base regulation and chemoregulatory $CO_2$ sensitivity." It is well-known that monoamine oxidase inhibitors, tricyclics, and alprazolam all alter lactate sensitivity in patients with panic disorder and that these patients do have a number of abnormalities in acid base regulation and $Pco_2$. No one knows whether these are primary or secondary. Hand and Wittchen's commentary and the chapter itself are misleading.

Ehlers, Margraf, and Roth write a useful review of most (but not all) of the data through 1985 on experimental reduction of panic attacks. They state that the data reveal that the actual increase from baseline in lactate levels is similar for panic patients and normal control subjects. Unfortunately, they come to this conclusion by relying heavily on two studies that are fatally flawed in design. These studies collected data at regular fixed intervals (5, 10, 15, 20 minutes) during lactate infusions or $CO_2$ inhalation. Other studies have shown that panic attacks do not occur at fixed intervals after lactate challenge; indeed, the mean peak panic point is 12 minutes after lactate infusion. Without measures at the "peak panic point," confident conclusions about panic attacks following experimental induction cannot be made.

Section three includes three studies on behavioral treatments for phobias with panic attacks. Once again, these studies contain unfortunate oversights. Hand and Wittchen state that all three involved abstinence from medication, but blood test screens for anxiolytics or antipanic drugs were not reported. This is a serious limitation, since it is well-known that 20%–25% of patients participating in anxiety studies, including psychopharmacology trials, take anxiolytics while stating they are abstaining. Drug screening tests should be mandatory in all behavioral treatment studies. Hand et al. consider that the most useful information from the studies comes from an analysis of patients with severe agoraphobia

who did or did not improve 1–4 years after behavioral treatment. Patients who improved showed significant additional follow-up effects on all variables, but those who did not showed no effects at all.

As proceedings of a conference in a supplement (perhaps two supplements) to one of the psychiatry journals, these papers would be more accessible through journal computer searches than they are as a book. Books are only rarely referenced in computer databases. Researchers planning anxiety studies may wish to get a copy of this book through interlibrary loan. I would not buy it. Most clinicians will find very little that they have not heard before or that will substantially alter how they treat the next anxious or phobic patient. In summary, this is really a book for behaviorists in need of a transfusion. Even then, caution is advised.

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**Panic and Phobias 2: Treatments and Variables Affecting Course and Outcome,** *edited by Iver Hand and Hans-Ulrich Wittchen. New York, Springer-Verlag New York, 1988, 265 pp., $89.50.*

This book is in many ways the best of a doubtful genre: a compilation of papers from a theme-oriented meeting. The topic is timely and reflects a controversial, rapidly developing area of knowledge. The authors are well-known, active researchers. The writing is usually clear and lively. Many methodological approaches are represented. The reader might well anticipate a good informative read.

The hallmark of a good scientific paper, however, is consideration of the shortcomings of the methods used as well as the merits of alternative hypotheses compatible with the results found in the context of the relevant literature. This compilation of papers is sadly typical insofar as many of the articles neglect such consideration.

To emphasize this crucial feature is not simply editorial fussiness. The goal of scientific communication should be not evangelism but an attempt to educate the reader, who is usually less knowledgeable than the author, about the pros and cons of a complex situation. Of the 23 chapters, few indicate the limitations of their particular approach.

A partial exception is the epidemiologic study by Wittchen, who points out the small total sample size, the very small number of patients necessary to test hypotheses about subgroups, and the fact that his sample was heterogeneous, "consisting of subjects with a variety of syndromes (panic, obsessions, depression and substance abuse) all known to affect in themselves course and outcome." Even here there is no criticism of the diagnostic instruments used or their clinical relevance, and one might well be concerned with their clinical validity because in five of Wittchen's 16 agoraphobic patients the reported age at onset was 10 years and these five patients, counterintuitively, did particularly well at 6-month follow-up.

Uhde and Stein present a useful clinical summary of pharmacological treatment and the evidence for biological disturbances of panic disorder. Concluding their review, which indicates a number of biological disturbances, they forthrightly state, "It remains unclear as to whether or not these biological markers represent primary abnormalities that are intimately related to the pathogenesis of panic disorder, or whether or not they merely reflect the secondary effects of chronic anxiety or 'stress.' There is a paucity of studies that have followed these biological markers serially over time, and we therefore do not know if they remain abnormal or remit with treatment." In general, the discussion by Uhde and Stein is distinguished for attempting to confront the varying viewpoints on the range of data.

In contrast, Mavissakalian hypothesizes that "the mechanism of action of imipramine consists of facilitating the therapeutic process of habituation underlying fear reduction." Strong hypothesis testing would cite literature that does not support this viewpoint, such as findings that imipramine has no beneficial effect on simple phobia, but this is not attended to.

In the sample described by Klosko et al., one-third of the patients in their waiting-list group did not develop panic attacks during the study period. The authors, however, do not reflect on any possible difficulties with their diagnosis of panic disorder for sample composition and generalizability.

There is a general lack of concern about the enormous power questions engendered by the ubiquitous small samples. Klosko et al., for instance, argue that their inability to distinguish alprazolam from placebo was not important because their sample values resembled the values found in the Upjohn cross-national study. This argument is vacuous because a wide range of values derived from small samples would not contradict values found in larger series. For instance, they report that 36% of their 11 placebo patients were panic free but do not note that the 95% confidence limits on this are 15% and 65%. Klosko et al. provide an example of tendentious handling of data, a lack of concern for alternative hypotheses, and unwarranted evangelism concerning therapeutic benefit.

Another example of a lack of concern for power issues is the otherwise very sophisticated article by Mathews, who points out, "The most popular method of assessing the effectiveness of anxiety management methods has been to use a straightforward comparison with a no-treatment condition." However, to investigate if there are specific ingredients within anxiety treatments "requires a comparison with an alternative condition, which is presented as an effective psychological treatment, but which excludes all of the specific techniques usually incorporated." He then reviews a study in which "approximately 20 patients" were allocated to each of three treatment conditions: anxiety management, nondirective counseling, or a waiting-list control group. His conclusion in reviewing this study is that "the different treatment approaches successfully influence the explanations given by clients for their improvement, but these do not correspond with real improvement differences." Further, the absolute amounts of clinical improvements seen on the central measures of clinical anxiety were relatively small.

Mathews reviews a second study, by Borkovec et al., which investigated whether a cognitive therapy added more to relaxation training than did nondirective counseling in 30 anxious students. The differential benefits of cognitive therapy were limited to self-report measures and did not extend to blind assessor ratings. Mathews also indicates that the student group may not have been representative of patients with anxiety disorders referred by general practitioners, who were the subjects of the first study he reviews.

A third study reviewed by Mathews, by Borkovec and Mathews, involved 30 patients with severe nonphobic anxiety disorders who received either cognitive therapy, nondirective counseling, or coping desensitization. In the currently popular coping desensitization condition, patients were required to imagine anxiety-provoking situations or to provoke related somatic sensations and then practice eliminating

anxiety using their relaxation skills before using the same techniques in real life. Mathews concludes that "there were no significant differences in outcome between the three different treatment conditions."

In his review of these three studies, Mathews considers the improvements obtained of similar magnitude to those obtained in other well-conducted studies. He then draws the following conclusions:

> (1) Anxiety management methods are consistently superior to no treatment. (2) None of the methods examined are clearly superior to non-directive counselling with representative clinic populations. (3) There is no convincing evidence that different anxiety management techniques act specifically on their presumed targets .... It would be wise to grasp the nettle, and consider the implications of the present negative findings, rather than reject them on the grounds that they do not fit our preconceptions .... Conceivably it makes little difference which particular technique each individual uses, whether this is relaxation, modifying automatic thoughts, or attempting to understand the underlying causes, as long as the previous exclusive focus on potential danger is modified.

Although I sympathize with these Jerome-Frank-like views, Mathews still should have considered the fact that the minuscule samples in each treatment generated extraordinarily low power. Therefore, his conclusions dubiously affirm the null hypothesis, i.e., since he could not find a difference there was no difference.

One could go on, but to sum up, "edited" compilations of short presentations are a risky smorgasbord and not to be confused with the products of peer review.

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## PERSONALITY, DISSOCIATIVE, AND SOMATOFORM DISORDERS

**Borderline and Narcissistic Patients in Therapy,** *edited by Nonna Slavinska-Holy, Ph.D. Madison, Conn., International Universities Press, 1988, 544 pp., $60.00.*

As a general psychiatrist who has long been interested in the psychotherapeutic treatment of borderline and narcissistic patients, I was drawn to the title of this book, but the reward of persevering through the text was limited. The book has 23 chapters, five of which are revisions of articles previously published elsewhere, by 27 different psychiatric, psychological, or psychoanalytic authors who refer to leading thinkers in the field such as Kohut, Kernberg, Modell, Masterson, Adler, and Gunderson. They present a wide array of creative clinical combinations of individual, couple, group, and family therapies.

Unfortunately, there is no integrative guide to assist the reader in placing these therapies in an overriding theoretical framework. Exceptions to this are Kibel's contrast of the descriptive use of borderline or narcissistic disorder in *DSM-III* with the high level of theoretical inference found in the systems of Kohut and Kernberg and the editor's brief discussion regarding whether borderline and narcissistic categories can be considered unique nosological entities or are best lumped together because of the binding commonality of the presence of the patient's lack of "authentic identity."

Wong describes the advantages of adding group therapy to individual therapy to deal with regressive transference and the need for identification models, but the contrasts between narcissistic and borderline patients do not come across clearly. Lachmann gives a picture of the developmental aspect of self psychology and the derivative therapeutic strategy of letting a stable self-object transference develop, but this is not applied differentially to narcissistic and borderline personality disorders. Magid summarizes the principles of treatment derived from self psychology, but his description of a patient with "borderline features" is confounded by indications that it illustrates the fluidity of the "borderline-narcissistic continuum." Hamm and Shapiro demonstrate how projective identifications in family therapy are worked through in such a way as to allow an adolescent girl with borderline disorder as well as her parents to proceed with their own development. Pines effectively differentiates borderline and narcissistic conditions in theory and interpersonal manifestations—the individual with narcissistic personality is able to make use of object relations to maintain a sense of pseudo-cohesion, in contrast to the cycle of acting out and regression so prominent in the course of borderline disorder. Durkin attempts to find common ground in narcissistic and borderline conditions as pathologies of "boundarying," but his attempt to apply general systems theory to group therapy is hard to follow.

Ulman gives a readable example of a transference-countertransference neurosis reflecting the therapist's need for the patient to serve as an "archaic mirroring self object," an "interplay between the patient's and therapist's developmentally arrested psychological structures."

In contrast to the chapters in part one, described above, where outcome is given in terms of clinical anecdotes, part two of this book contains reports of several objective studies. For example, Hofheimer and Apprey present data on the effects of borderline mothers' perception of, interaction with, and developmental effects on their infants.

This book is not recommended for the novice. For the reader looking for a new combination in psychological treatment of these disorders, however, this book would be of some value. The case material is elucidating, and the emphasis on the problem areas of transference, countertransference, projective identification, and timing of therapeutic mirroring or interpretation can add breath, perhaps wisdom, and even a "soothing experience" for the struggling therapist in the field.

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**Treatment of Patients in the Borderline Spectrum,** *by W.W. Meissner, S.J., M.D. Northvale, N.J., Jason Aronson, 1988, 614 pp., $55.00.*

Dr. Meissner is to be commended on his thorough discussion of the competing philosophies of psychotherapy that have developed over the years regarding patients with borderline personality disorder. Meissner's own approach draws heavily on the work of Kernberg, the British object relations school, and Buie and Adler. His strong preference for an analytically oriented mode of psychotherapy comes through in these pages. Meissner is nonetheless firm in advocating an integrated approach, stating that "particularly in the treat-

ment of borderline patients, where considerable variability and instability is so often a feature of the clinical situation, the therapist needs to maintain a position of flexibility and adaptability, allowing the selection of available techniques from the range of psychotherapeutic interventions to deal with the problems presented" (p. 121).

Readers who are familiar only with the *DSM* definition of borderline personality disorder will need to make adjustments if they are to absorb the material Meissner presents, since he uses the term "borderline" more in the broadly defined manner of Kernberg. His opinion that "at least some borderline patients are potentially analyzable" would be much more defensible within the realm of Kernberg's criteria than within the context of *DSM-III-R*.

Meissner pictures borderline patients as occupying various positions along a spectrum (reminiscent of Grinker's types I to IV) with respect to level of impairment. The distinctions he makes have clinical utility; the treatment approach toward patients with severe and chronic impairments must clearly be different from that toward patients who come near the border with the mild "psychoneuroses" (a term no longer accepted in *DSM* but in wide use within the analytic community). Diagnostically, Meissner divides borderline disorder along two continua—the hysteric and the schizoid. I find these a narrow set of choices. The dysphoric personality ends up along the hysteric track, which seems a bit forced; I suspect that phenomenologically it deserves a separate track.

One of the more original and welcome aspects of the book is in the final section, The Patients, where Meissner offers some 25 vignettes of patients of differing diagnostic and prognostic types. Meissner offers failures as well as success stories. All too often, writers on the subject discuss their successes at great length, leaving the reader with the impression that with enough wizardry all borderline patients can be helped by any given therapist. Meissner deserves credit for affirming through his own shared experience that this is clearly not the case. Many of the patients who quit abruptly or did not do well had been victims of abuse during their earlier years. Meissner alludes to this in passing; one might wish he had dwelt at a greater length on this history, which we are recognizing more and more as an important factor in borderline disorder. Also, since only about half of the cases seem to meet *DSM* criteria, one could have wished Meissner had presented a table outlining specifically which patients would have been diagnosed as borderline by *DSM*, by Gunderson, and by Kernberg criteria.

Although long-term analytically oriented psychotherapy and classical psychoanalytic techniques are applicable only within a certain range of the totality of borderline disorder, Meissner's book constitutes a humanistic, balanced, and refreshing addition to the literature on this subject.

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**Diagnosis and Treatment of Multiple Personality Disorder,** *by Frank W. Putnam. New York, Guilford Press, 1989, 351 pp., $35.00.*

One of the most intriguing phenomena in contemporary U.S. psychiatry is the emergence of multiple personality disorder from the realm of conditions deemed to be exotic, extinct, or even apocryphal into the mainstream of clinical awareness. Seen without the distortions of countertransferential fascination on the one hand or countertransferential skepticism on the other, it stands revealed as a complex and chronic posttraumatic dissociative psychopathology, the sequel of an overwhelming childhood, usually one fraught with severe and sustained child abuse. Shorn of its drama, it becomes comprehensible as a beleaguered child's attempt to adapt to intolerable circumstances. These recognitions do much to demystify multiple personality disorder and to advance its rational study.

Although multiple personality disorder is recognized with increasing frequency, its treatment often proves challenging in the extreme and often leaves the psychiatrist feeling confused and deskilled. Although the literature of this field has begun to grow, and a specialized journal (*Dissociation*) is now available for those with particular interest in such patients, the clinician encountering his or her first case of multiple personality disorder has not had a single resource to serve as a guide and reference. Frank W. Putnam has provided such a text and done so in such a comprehensive and masterful manner that *Diagnosis and Treatment of Multiple Personality Disorder* has from the moment of its publication become the standard in the study of dissociative disorders.

Simply stated, Putnam has succeeded in rendering the often-confusing field of multiple personality disorder comprehensible and accessible to the mental health professions. He has done so in a lucid and pragmatic manner that draws on his exposure not only to the scientific literature but also to the "oral literature" of workshops involving therapists with experience with multiple personality disorder who were struggling to assist these patients long before the current renaissance of interest in this condition. The result is a book of impressive depth as well as breadth and of a surpassing pragmatism free of the imposition of paradigms that, however congenial, have little to do with the thrust of recent findings.

Putnam reviews the history of multiple personality disorder and of attempts to define it; reviews issues of etiology, epidemiology, and phenomenology; and offers a practical approach to diagnosis. Although the chapters on these subjects are excellent, the major strength of the book resides in the seven chapters on treatment, which overflow with practical advice and clinical pearls. Putnam is especially sensitive to the circumstances of the clinician confronting his or her first case of multiple personality disorder and takes pains to anticipate and respond to recurrent common difficulties. Since until now much of this valuable information was available only through workshops and supervision or had to be learned by painful experience, this book should be regarded as indispensable for the clinician confronted for the first (or the hundredth) time with a patient who has multiple personality disorder.

Putnam succeeds in his objective of making a balanced presentation of the issues encountered in the psychotherapy of patients with multiple personality disorder; his book is a monumental achievement in this. Because its focus is quite different from that of other related publications, it does not replace them. The reader of this book will find much of value in texts such as Braun's *Treatment of Multiple Personality Disorder* (1), which addresses a different cluster of topics.

Some minor cautions must be added in the face of my overall positive regard for this book. Because Putnam takes pains to be impartial, he often mentions a number of alternative views or advice, giving them the appearance of equal weight. The reader who is not familiar with the literature on multiple personality disorder may not appreciate that the bulk of experience and the consensus in the field may favor one of these options over another. In addition, Putnam, in

drawing from his own experience, inevitably offers some opinions that are at variance with those of other authorities in the field. Since Putnam's opinions are invariably thoughtful, this is not a major difficulty, but the reader must bear in mind that this is a new field in which much remains to be established. A minor criticism, of little moment to the general reader, is that, much as Putnam anticipates in his preface, an occasional attribution of credit for contributions from the "oral literature" of the field of multiple personality disorder is problematic.

In summary, for the psychiatrist who is contemplating the purchase of a book on multiple personality disorder for his or her library, this book would be an excellent investment.

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**Self-Mutilation: Theory, Research, and Treatment,** *by Barent W. Walsh and Paul M. Rosen. New York, Guilford Press, 1988, 273 pp., $30.00.*

Who among us has not suffered the anguishes of working with the wrist cutter or the patient who excoriates himself with cigarettes or the intractable head banger? To treat these patients is to be confronted with a variety of pathologies, from organic to characterologic. And to heal such patients requires the firmest hold on milieu and countertransference issues as they inevitably emerge.

*Self-Mutilation* by Walsh and Rosen attempts to shed light on the phenomenologies of this disease process. Focusing on theory, research, and treatment, the authors differentiate suicide from self-mutilation and then go on to describe mutilation in different groups, including adolescent, psychotic, and retarded and autistic patients. A chapter reviews the problem of contagion, and treatment chapters review psychoanalytic and family and group therapy. The tone of the book is investigative; although the authors (about whom there is no identifying information) describe their own treatment efforts with patients, they tend to use psychological theory to explain clinical phenomena:

> Suicide and self-mutilation are most alike in their most general or global characteristics. Both suicide and self-mutilation are the result of frustrated psychological needs, and both reflect lifelong coping patterns. Yet even in these facets the behaviors are different: (1) The unmet needs of self-mutilators seem to be more short-term, involving deferment, rather than a long-term, continuous frustration of needs; and (2) the lifelong, coping patterns of self-mutilators remain on a basic level "adaptive" in that these individuals chose disfigurement over cessation. (p. 51)

I liked the contagion chapter best and the treatment chapters less, primarily because the authors chose not to discuss the range of psychopharmacological treatments. Although there is obviously no one drug for aggression, drugs play a crucial role in the reduction of certain forms of self-injury due to altered psychotic thinking or even due to organicity. This is a major omission. I would also have liked to read more about countertransference issues in treatment.

This book must be compared with two existing others, one of which, *Self-Mutilation* by Ross and McKay (1), is often cited by the authors. Ross and McKay write in a style similar to that of Walsh and Rosen with an emphasis on the psychology of events. In contrast to both these texts is *Bodies Under Siege* by Favazza and Favazza (2), a broad and rich text that ranges from the anthropology of self-mutilation to diverse clinical patient groups at risk. Favazza and Favazza's didactic text is smoothly interspersed with case examples, a tribute to the authors' expertise and intrigue with the topic. In contrast, Walsh and Rosen's work is more sterile and difficult to read, yet nonetheless reflective of a major attempt to organize knowledge about this difficult subject.

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# Letters to the Editor

### Exacerbation of Symptoms of Multiple Sclerosis in a Patient Taking Fluoxetine

SIR: I wish to report an apparent exacerbation of the symptoms of multiple sclerosis associated with the use of fluoxetine. Such an occurrence is apparently rare (Eli Lilly and Co. reported to me on the telephone that they had two other possible associations in their database of adverse reactions) and has not been reported in the literature to my knowledge.

Ms. A, a 41-year-old single white woman, had symptoms of fatigue and numbness in her nondominant forearm and hand that were diagnosed as multiple sclerosis about 7 months before she began fluoxetine therapy. A magnetic resonance imaging scan supported the diagnosis. The patient had a long history of moderately severe depressions, although she had never been hospitalized and had functioned well in high-level professional positions. For several months she had experienced great difficulty obtaining work; she was becoming panicked about whether she would be able to find any work and had begun ruminating about her worth.

Fluoxetine was started, and approximately 10 hours after the first dose, Ms. A began experiencing an exacerbation of the numbness in her arm and the "grogginess" she associated with her multiple sclerosis. These symptoms were initially mild but progressed over the next 4 days while she continued the medication. By the fourth day, she was sufficiently alarmed to discontinue the medication and report her symptoms. Over the next 3–4 days, after discontinuation of the fluoxetine, these symptoms returned to baseline. The patient has not been rechallenged. While this association may have happened by chance or been idiosyncratic, there seems to be a possibility that fluoxetine exacerbates symptoms of multiple sclerosis.

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### Toxicity of Fluoxetine in Overdose

SIR: Fluoxetine, a selective serotonin uptake inhibitor, appears to be generally a safer alternative to tricyclic antidepressants in the treatment of major depressive disorder (1). As psychiatrists use this medication with increasing frequency, there is a need to know the potential side effects that can occur in depressed patients who attempt suicide with overdoses of their antidepressant medication. To date, there have been only a handful of reported cases of fluoxetine overdose, and all have occurred in combination with other drugs. The following case report describes a woman who made a planned, intentional suicide attempt by ingesting 2000 mg of fluoxetine alone.

Ms. A, a 39-year-old woman, was a chronic overachiever who had had one hospitalization for major depression but had made no prior suicide attempts. She admitted to ingesting all the antidepressant medication that she had purposely hoarded in her kitchen cupboard for several months in an intentional suicide attempt. After about 2 hours she became nauseated and vomited several times before calling a friend, who corroborated the patient's actions by bringing to the emergency room four empty bottles of fluoxetine, representing approximately 100 20-mg capsules, discovered at the scene. In the emergency room, 1 hour later, Ms. A's vital signs were blood pressure, 100/70 mm Hg; pulse, 78 bpm; respirations, 18/min; and temperature, 97.5 °F. A physical examination revealed a patient who complained of nausea and nervousness but who otherwise appeared to be in no acute distress. The remainder of the results, including those of all laboratory tests (CBC, electrolytes, and hepatic and renal panels), were unremarkable. Gastric lavage revealed no pill fragments. Repeated checks of vital signs and ECGs demonstrated no abnormalities. Ms. A was then transferred to the psychiatry service, where she had an uneventful recovery and was discharged a few days later.

Our case indicates, as do the report of Wernicke (1) and the case of Finnegan and Gabiola (2), that the toxicity of fluoxetine in overdose is much less than that of the commonly prescribed antidepressants.

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### Fluoxetine Treatment of Exhibitionism

SIR: Exhibitionism, according to *DSM-III-R*, is a disorder in which there are recurrent intense sexual urges and sexually arousing fantasies involving the exposure of one's genitals to an unsuspecting stranger. The patient either experiences marked distress or acts on these urges. These criteria bear a marked resemblance to features of obsessive-compulsive disorder.

Mr. A, a 32-year-old Caucasian man, was admitted to the hospital after attempting to hang himself because of disturbing thoughts of exposing himself to children. He stated he had been bothered by thoughts of exposing himself to female children most of his life and in fact had recently exposed himself in a local department store

elevator. Exposure was usually followed by public masturbation. He had a history of such behavior since early childhood and had had multiple arrests and psychiatric hospitalizations. At age 22 he was diagnosed as suffering from schizophrenia and had been treated since that time with various neuroleptic and tricyclic regimens, with no relief from the exhibitionistic symptoms. He had also been previously unsuccessfully treated with medroxyprogesterone injections for exhibitionism.

On admission the patient was taking fluphenazine, 50 mg/day. This was discontinued, and the patient was observed before further pharmacotherapy. During this time he continued to complain of fantasies involving genital exposure. He was started on fluoxetine, 20 mg/day, and several days later the dose was raised to 40 mg/day. He gradually complained less of such fantasies but began complaining of "seeing blood on people's faces" and developed mild thought disorder. He was started on fluphenazine, 10 mg/day. Over a 3–4-week period he experienced fewer thoughts of exhibitionistic behavior. He was discharged somewhat improved.

Two months later Mr. A was readmitted because of severe dystonia secondary to a change in neuroleptic dose by his outpatient psychiatrist. During the preceding 2 months he had shown no exhibitionistic behavior. He reported significant relief of his exhibitionistic fantasies for the first time since early childhood. It was felt this was a positive response to the fluoxetine.

Exhibitionism may have pathophysiologic mechanisms similar to those of obsessive-compulsive disorder in that intrusive thoughts are present, which are distressing, and relief occurs by compulsive behavior. This patient appears to have responded to fluoxetine, which is effective in treating obsessive-compulsive disorder. Although this is a single case report of the first such patient I have treated in this manner, the response was impressive. The etiology and treatment of this disorder deserve further study and clarification.

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## Mania in a Panic Disorder Patient Treated With Fluoxetine

SIR: Fluoxetine, a recently introduced antidepressant, is useful for the treatment of panic disorder as well as major depression and other disorders, such as obsessive-compulsive disorder. Like most antidepressants, it has also been associated with the precipitation of mania in patients with mood disorders. To my knowledge it has not, however, been reported to precipitate mania in patients with panic disorder without coexisting mood disorders. I present such a case.

Mr. A, a 40-year-old man, had suffered from panic disorder for 5 years. He had been treated with supportive psychotherapy and alprazolam, 0.25 mg p.r.n., until his symptoms increased after 3½ years. When he was referred to me, I prescribed nortriptyline for panic attacks. There were no signs or symptoms of depression at any time during his treatment. Doses of nortriptyline higher than 85 mg h.s. resulted in unacceptable side effects, but at this dose his panic attacks ceased, and he began driving a car again. Mr. A still experienced occasional limited-symptom attacks and was also treated with alprazolam, 0.50 mg p.r.n. After 16 months, however, he insisted on a change of medication because of a 20-lb weight gain. Fluoxetine, 20 mg/day, was started, and the nortriptyline was gradually tapered. His panic symptoms remained in remission, and in addition he reported complete cessation of his limited-symptom attacks and anticipatory anxiety.

About 11 weeks after starting fluoxetine and 4 weeks after discontinuing nortriptyline, Mr. A became manic, with pressured speech, racing thoughts, distractibility, hyperactivity, expansive mood, and grandiosity. He spent thousands of dollars on unnecessary repairs at his place of business, had grandiose marketing plans, discussed new inventions he was working on, and stated he would run for governor were it not for "the skeletons in my closet." He spent hours on the telephone offering exceptional favors to anyone who called.

Mr. A's psychiatric history did not include any previous episodes of mania or depression. A paternal uncle had been psychiatrically hospitalized for 1 year for an unknown disorder, and a sister may have had obsessive-compulsive disorder.

Mr. A's fluoxetine was discontinued, the alprazolam was increased, and the episode subsided in 2 weeks. He was subsequently restarted on fluoxetine, 20 mg every other day, without recurrence of panic symptoms.

In clinical trials, mania or hypomania occurred in 46 of 5,920 patients (0.78%) treated with fluoxetine, compared with three of 733 (0.41%) tricyclic-treated patients (personal communication, Dista Products Co., September 1989). Other studies indicate that rates of conversion to mania or hypomania with fluoxetine are similar to rates with tricyclics (1). Although five cases of mania associated with fluoxetine have appeared in the literature (personal communication, Dista Products Co., September 1989), none were in patients with panic disorder. While nine cases of alprazolam-induced mania in patients with panic disorder have been reported (2), no reports of cases associated with tricyclics, heterocyclics, or monoamine oxidase inhibitors were uncovered in a MEDLINE search.

The relationship of mania to the use of fluoxetine rather than alprazolam, which the patient had used for 5 years and the dose of which was *increased* in the presence of mania, would seem to rule out alprazolam as the provocative factor.

Although mania and hypomania have sometimes been regarded as side effects of antidepressants independent of an underlying bipolar mood disorder, the comorbidity of panic with major depression and the strong relationship between the two disorders in some family studies (3) suggest the possibility that some patients with panic disorder, who may therefore be genetically at risk for a major mood disorder, are also susceptible to drug-induced mania. Further experience with fluoxetine and other antipanic drugs may clarify this issue.

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## Bupropion in Chronic Fatigue Syndrome

SIR: In the past few years, there has been continuous progress in the study of interrelations between depression and the immune system (1–3). A series of papers have indicated that measures of lymphocyte stimulation by mytogens (1, 2) and natural killer cell activity (3) are significantly lower in severe major depressive disorder.

Just as impaired immunity has been seen in depression, so have there been depression-related findings in immune disorders. Chronic fatigue syndrome is a recently described disorder of immunity with symptoms of frequent infections, fevers, and impaired immunity combined with extreme fatigue and lack of motivation (4). We present two cases in which the unique new antidepressant bupropion produced rapid relief of all symptoms at minimal dosages.

Ms. A, a 61-year-old white woman, had an 8-year history of frequent upper respiratory infections, low-grade fevers, and overwhelming fatigue. Previous attempts at treatment with both doxepin and fluoxetine had failed. Her immunology workup included +3 levels of circulating antibody to *Candida*, positive Epstein-Barr virus titers, and T suppressor/cytotoxic cell depletion (10.6% of total leucocytes; this is roughly 30% below the normal range of 15.2%–41.6%). After 1 week of taking 100 mg b.i.d. of bupropion, Ms. A had a complete remission of symptoms; her score on the Beck Depression Inventory dropped from 18 to 0. Her respiratory infections, fevers, and fatigue disappeared. At this low dose of bupropion, there was no return of any symptoms in the following 6 months.

Ms. B, a 48-year-old white woman, had a 10-year history of upper respiratory infections, fevers, and chronic fatigue to the point that she was bedridden. Her symptoms had previously been unresponsive to imipramine, amitriptyline, doxepin, and amoxapine. Among other findings, her Epstein-Barr virus titer was 1:160 with high antibody titers to *Candida*. Two weeks after she had started to take 100 mg t.i.d. of bupropion, her Beck depression score dropped to 7 and her symptoms cleared. In the following 3 months, there was no return of any symptoms despite major environmental stressors, including loss of her job and her boyfriend.

These two cases of substantial response of chronic fatigue syndrome to bupropion suggest that further clinical research should be directed at its use in controlled trials. Bupropion has been described as particularly effective in depression characterized by extreme fatigue and hypersomnia (5), and a dopaminergic mechanism of action has been proposed. If controlled research replicates these findings, it might suggest that dopaminergic deficiencies are directly related to the impairments in immunity found in major depression. Certainly, such a research plan should initially proceed with an open study of response of depression ratings to bupropion, combined with prestudy and poststudy measures of Epstein-Barr virus titers and natural killer cell activity, to be followed by other studies with double-blind assessments of clinical improvement.

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## Pharmacologic Approach to Sleep Panic Attacks

SIR: Thomas A. Mellman, M.D., and Thomas W. Uhde, M.D., recently reported on the phenomenon of sleep panic attacks (1). The case report that follows confirms their clinical findings and also describes a specific pharmacologic approach to this problem.

Ms. A presented at age 23 with a several-month history of daily spontaneous daytime panic attacks, dysphoria, insomnia, and anorexia. She was treated with imipramine, 125 mg/day. Within 6 weeks her panic attacks had decreased to once or twice monthly, and her dysphoria, insomnia, and anorexia resolved. Her condition remained stable for approximately 1 year, at which time she noted a slight increase in the frequency of her daytime panic attacks, along with the onset of sudden nocturnal awakenings that occurred several times a month. These awakenings were associated with extreme fear, palpitations, and diaphoresis but not with any dream recall. Ms. A's blood level of imipramine plus desipramine was found to be 232 ng/ml. Because of this relatively high level, it was decided not to increase her dose of imipramine but, rather, to add potentially synergistic agents. Lorazepam, 1 mg in the morning and at bedtime, was added but was of minimal benefit. On the basis of the knowledge that lithium carbonate is frequently beneficial when added to a tricyclic antidepressant in resistant unipolar depression (2), lithium carbonate, 900 mg h.s., was then added to Ms. A's medication regimen. Within 10 days the patient's nocturnal awakenings, as well as her daytime panic attacks, had ceased. She continued taking lithium for 2 months with good results. Lithium was then discontinued, and within 3 days her nocturnal awakenings and daytime panic attacks returned. After lithium had been discontinued for 1 week, it was restarted at the previous dose. Within 7 days her nocturnal awakenings and daytime panic attacks again ceased. Ms. A has continued to take a combination of imipramine and lithium for 6 months without any recurrence of nocturnal awakenings or daytime panic attacks.

Previous descriptions of the phenomenon of sleep panic attacks (1, 3) are identical to my description of this case. However, this case report is unique in its longitudinal description of the development of sleep panic attacks relatively

late in the course of the patient's panic disorder. The sleep panic attacks appeared to be an extreme symptom of the panic disorder, which was resistant to standard antipanic medication (imipramine and lorazepam) but responded to the addition of lithium to the imipramine. The response of tricyclic-antidepressant-resistant panic disorder to the combination of a tricyclic and lithium has heretofore been reported only to a limited extent (4, 5).

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## Erotomania and Senile Dementia

SIR: Secondary erotomania has been associated with many psychiatric syndromes but, to my knowledge, there has been only one report of erotomania associated with senile dementia (1). I would like to add another case to the small literature.

Ms. A, a 77-year-old widow, was admitted to the hospital for investigation of obsessive and delusional thoughts. She was convinced that she was loved by a priest whom she had met at a relative's funeral some 6 months earlier. She persistently and inappropriately telephoned him, and before admission she had attempted to stop cars in search of someone to drive her to his community. She also believed that they had been married for the past 2 months, in spite of her family's denial. She would explain his absence by stating that he was away at a retreat.

During the past year there had been gradual deterioration in Ms. A's memory and level of general functioning. She was apathetic, lacked motivation, and had lost interest in her hobbies and daily housework. There was no mood disturbance. She stopped attending a community group of which she had been a member for 15 years, asserting that they were not paying enough attention to her. Significantly, 8 months before her admission, her landlady, with whom she socialized, was hospitalized.

Ms. A had no previous psychiatric history; her medical history included obesity, hypertension, hyperlipidemia, osteoarthrosis, and psoriasis, all adequately controlled. On examination she was a very pleasant woman whose dress showed self-neglect. There was neither mood disturbance nor formal thought disorder. Her only delusions were those concerning the priest and her "power to heal diseases." She initially scored 27 out of 30 on the Mini-Mental State examination (2). A subsequent comprehensive organic workup, including cerebral CT scan, was essentially normal. An occupational therapy assessment was satisfactory, but the nursing staff reported that Ms. A was forgetful and had difficulty locating her room; otherwise, she needed minimal assistance for activities of daily living.

Further psychological testing, including the Hooper Visual Organization Test (3), the Reitan-Barter, and the Rorschach, was pursued, and the results were all highly suggestive of mild to moderate dementia. Ms. A was treated with a neuroleptic for her erotic delusions, but there was minimal response. She was referred to community home services for supervision.

On initial assessment the *DSM-III-R* diagnosis of delusional disorder, erotomanic type, seemed to fit Ms. A well. She also presented interesting possible psychodynamic issues, as elaborated in a recent review of erotomania (4): 1) the need for narcissistic gratification and approval, 2) a defense against unconscious homosexual wishes toward her landlady, or 3) a pathological mourning, as she had met the priest at a funeral.

Although she had scored fairly well on the Mini-Mental State examination, her age, her lack of previous psychiatric history, the gradual deterioration in her level of functioning over the past year, and her forgetfulness as observed by the nursing staff prompted further testing to eliminate an organic origin. Erotic delusions arising late in life should be thoroughly investigated to rule out organicity.

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## Please, No More "ECT"

SIR: A recent headline in the *New York Times* read, "Electroshock Is Effective and Safe, Defenders Say" (1). A headline in a South Carolina newspaper (2), also occasioned by the completion of the report of the APA task force on ECT (3), proclaimed, "Shock Therapy Endorsed: Study Says It Works in Some Depressive Cases." After 50 years the treatment still seems to require defenders and another study to prove that it works. The popular name itself is shocking and makes too good a headline. "Electroconvulsive therapy," although better, is not nearly far enough removed from "shock therapy." The terms are specters from the past, when the procedure was indeed frightening because it was used without general anesthesia and was often abused. It is time to relegate those facts to the historical archives where they belong. They have no relevance for psychiatric practice in the 1990s.

Knowledgeable people can no longer doubt the safety and efficacy of an electrically induced seizure under general anesthesia for the treatment of severe depression. And few who have firsthand knowledge of how the treatment is adminis-

tered think it anything other than a modern, humane therapy for a group of very serious illnesses. ECT has multiple, potent effects on several neurotransmitter systems, although which of these is the critical one is not yet known. The September 1989 issue of *Convulsive Therapy* was completely dedicated to the mechanism of action of ECT. It contains a wealth of data, as well as theoretical formulations about how the treatment exerts its antidepressant effects. We know a great deal about how seizures affect the brain, and our knowledge is increasing rapidly, thanks to the efforts of several research groups around the country.

We suggest that the name "electroconvulsive therapy" must be changed in order to make a break with the past. The treatment in the hands of modern psychiatrists is fine; the name is archaic. Just as nuclear magnetic resonance has been changed to magnetic resonance imaging to avoid confusing and frightening our patients, so the name for ECT should be altered. In no other way, we believe, can the baggage of the past be left behind where it belongs.

What should the new name be? We suggest that it refer to the brain, since we know that the brain is the site of the treatment's action. We suggest, as well, that it make no reference whatsoever to electricity or seizures. Following the cardiologists' use of "cardioversion" as a model, we have considered many names, including "cerebroregulatory stimulation" (CRS) and "neurothymic stimulation" (NTS). We have not, however, hit upon what we consider exactly the right choice and hope that our creative colleagues may come up with a suitable term.

The APA task force report on ECT will do much to promoter better clinical practice and a deeper understanding of the treatment. However, it is likely that thousands of seriously depressed people will still suffer needlessly because of their misconceptions about the procedure. We suggest that the time has come to cease frightening our patients and stop doing electroconvulsive therapy; that is, stop using the name, not the treatment.

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## Neuroleptic Drugs and the Sigma Receptor

SIR: It has become axiomatic in schizophrenia research and treatment that antipsychotic drugs (neuroleptics) act by blocking dopamine ($D_2$) receptors. The three classic arguments supporting a central role of dopamine in schizophrenia and in neuroleptic drug action are as follows: 1) all clinically available neuroleptics block dopamine receptors, 2) treatment with neuroleptics leads to changes in dopamine content and dopamine receptors in the brain, and 3) the average clinical doses of neuroleptics correlate inversely with the affinity of the drugs for dopamine receptors.

Reasons to question the first two arguments include the observations that only those new compounds which demonstrate $D_2$ receptor-binding activity are evaluated further for antipsychotic potential and that neurotransmitter systems other than those which use dopamine are affected profoundly by administration of neuroleptics (1). The third point, that the clinically effective doses of antipsychotic drugs vary inversely with their affinities for $D_2$ receptors, may be subject to further interpretation for reasons that have not been discussed previously.

In the original reports that demonstrated this correlation (2, 3), $D_2$ receptor binding was assayed by using [$^3$H] haloperidol and [$^3$H]dopamine as ligands. In one study (2) the inverse correlation of clinically effective dose and receptor binding affinity was obtained with [$^3$H]haloperidol ($r=0.87$) but not with [$^3$H]dopamine ($r=0.27$). A qualitatively similar unspecified difference between [$^3$H]haloperidol and [$^3$H]dopamine binding was reported in the other original study (3). The sigma receptor, now regarded as a potential site of action for antipsychotic drugs and psychotomimetic benzomorphans, was first identified as a binding site for [$^3$H]*N*-allylnormetazocine (4). Haloperidol, which binds to several putative neurotransmitter receptor sites, has especially high affinity for the sigma receptor (5), and many studies use [$^3$H]haloperidol to label sigma receptors. In light of these more recent discoveries, the data presented in the seminal reports of Creese et al. (2) and Seeman et al. (3) may be interpreted as indicating that the average daily doses of antipsychotic medication correlate strongly with sigma but not $D_2$ binding.

Several new antipsychotic drug candidates share with haloperidol a high affinity for the sigma receptor, which is often greater than these drugs' affinities for $D_2$ dopamine receptors. Of course, it should also be noted that in vitro binding affinity may not always reflect in vivo therapeutic efficacy, especially for drugs such as the phenothiazines, which are metabolized extensively. However, several recent studies done at the Department of Psychiatry, Dartmouth Medical School, have shown that phenothiazine antipsychotic drugs are metabolized in humans to compounds which interact with sigma receptors. Potential molecular mechanisms of antipsychotic drug action must also take into account the multiple transmitters and modulators that may be localized with dopamine at synapses of potential interest in schizophrenia. This is certainly not to say that dopaminergic mechanisms have no role in psychiatric disorders but, rather, that in the advance of research in this area, it is best to maintain an open mind regarding antipsychotic drug action in schizophrenia and the etiology of schizophrenia itself.

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## Bipolar Affective Disorder and Heterozygous β-Thalassemia

SIR: Several years ago Joffe et al. (1) reported a possible association between thalassemia minor (heterozygous β-thalassemia) and affective illness in members of a limited pedigree. In another preliminary study Scherer and Eberle (2) found that patients with both depressive disorder and heterozygous β-thalassemia may show some peculiarities in symptoms. We have performed hemoglobin electrophoresis in 180 consecutive psychiatric outpatients given diagnoses according to the Research Diagnostic Criteria. The prevalence (17.8%) of heterozygous β-thalassemia (hemoglobin $A_2$ more than 3.2%) in the overall sample was within the range found in the general population in southern Sardinia (3). However, a trend for a greater prevalence was found in bipolar (including manic schizoaffective) patients (22.4%) than in unipolar patients (9.1%). Moreover, patients suffering from schizoaffective disorder with a bipolar course showed a significantly higher proportion of the hematological disorder than patients with other affective disorders (14 of 45, or 31.1%, versus 17 of 126, or 13.5%; $p<0.01$). We are now extending the original sample and studying the relatives of our probands. A false association due to population stratification will be excluded if cosegregation within pedigrees is found.

Whatever the genetic relationship between affective disorder and heterozygous β-thalassemia (false association, epistatic genetic interactions, linkage disequilibrium, direct effect), we would like to suggest the use of this easily diagnosable condition in linkage studies of affective disorders, since the β-globin gene cluster can be regarded as a polymorphic locus in certain populations and can help clarify the status of genetic linkage between bipolar illness and chromosome 11 (4, 5).

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## Seasonal Affective Disorder and the Photic Sneeze Response

SIR: Seasonal affective disorder is a condition usually characterized by recurrent episodes of depression in the fall and winter alternating with nondepressed or hypomanic periods in the spring and summer (1). It appears responsive to treatment with bright artificial light, although neither the pathophysiology of the disorder nor the antidepressant mechanism of phototherapy is well understood. However, Wehr et al. (2) have shown that phototherapy probably works through the eye rather than the skin. It has been hypothesized that seasonal affective changes are associated with a heightened vulnerability to fluctuations in environmental light (1).

To the best of my knowledge (personal communication from D.A. Oren and N.E. Rosenthal, Aug. 24, 1988), no one has yet noted the analogy between this vulnerability and another phenomenon involving heightened sensitivity to fluctuations in environmental light, namely, the so-called photic (or solar) sneeze reflex. This is the tendency to sneeze when suddenly exposed to bright light, a trait probably influenced by genetic factors (3). Everett (3) hypothesized that the photic sneeze reflex may be due to hypersensitivity of the parasympathetic nervous system. Dilsaver and Majchrzak (4), noting that depression may involve supersensitivity of a central muscarinic mechanism, found evidence that bright light subsensitizes central muscarinic function in rats. These preliminary data suggest that there may be a similar underlying cholinergic mechanism in the photic sneeze response and the sensitivity of the CNS to bright light generally.

I believe that further research to test this heuristic hypothesis is merited. For example, do individuals who show the photic sneeze response—probably about 20% of the general population—also show seasonal fluctuations in mood? Are there fast and slow loops by which bright light affects the CNS—the former represented by the photic sneeze reflex, the latter by vulnerability to seasonal affective disorder? Is there a common pattern of inheritance for these hypothesized loops? Provided that large numbers of individuals are tested, we should be able to answer these questions with fairly simple tests and questionnaires. An association between the photic sneeze response and seasonal affective disorder could have important therapeutic implications.

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## The Sham of Treatment

SIR: A recent lecture on the pharmacotherapy of schizophrenia by an outstanding expert consisted of lengthy, tedious, and repetitious presentations of slides showing the

significant differences between psychoactive drugs and placebos and also between clozapine and earlier antipsychotics. These data were based on symptom and behavioral changes assessed reliably in a double-blind manner and subjected to rigorous statistical methods. The symptoms and behaviors thus measured were not presented, implying that everybody knows what symptoms and behaviors patients with schizophrenia manifest.

This simplistic presentation of complex conditions and processes may be a caricature, but it is symptomatic of the neuropsychiatric paradigm (1) and current psychiatric treatment, whose nature and length are increasingly dictated by public or private third-party payers, by utilization review bodies, and by the unfortunate tendency (borrowed from internal medicine) to treat diseases instead of patients. This has been the unwelcome aspect of the so-called remedicalization of psychiatry, because medicine has abandoned Peabody's injunction that "the care of the patient lies in caring for the patient" (2) or, to quote a latter-day colleague emphasizing that communication is the main tool of the physician, "What the scalpel is to the surgeon, words are to the clinician" (3). Communication—exploring a person's feelings and thought processes—can also be "scientific" (4), but currently, on wards and in clinics, students and residents are taught to put symptoms and behavioral manifestations together into a cluster that fits one or another *DSM-III-R* definition, and by implication they come to believe that this tells them what treatment, and particularly what medication, to prescribe.

The excellent publication of the joint task force of the Association for Academic Psychiatry and the American Association of Directors of Psychiatry Residency Training (5) concerning psychotherapy training in the future did not address (it was not charged to do so) the essence of psychiatric education, which is to learn about people, about personality development and structure and their deviations, none of which can be apprehended by categorizing symptoms, but which requires psychotherapeutic engagement over time. It takes more than 3 weeks to learn about and understand a severely psychotic patient and gather data from families and others.

There are intangible impediments to interpersonal therapeutic engagement with psychotic patients. It is more comfortable to subdue a patient's excitement and unwelcome behavior chemically than to engage that uncooperative and possibly dangerous patient. Medication may be indicated but should not be prolonged without efforts to communicate with the person who is so fearsomely disturbed, although ultimately the patient may benefit from medication maintenance. The ease of dispensing drugs—which, by implication, may be believed to be "specific" because we have different pharmaceuticals for schizophrenic and depressed patients—leads to forgoing psychosocial and psychotherapeutic engagement. Such treatment may seem efficient and cost-effective in the short run, but it is not so in the long run, as indicated by our enormous readmission rates, and treatment and education suffer. It is more expensive to allow sufficient time and bring to bear appropriate professional resources for all inpatients than to discharge them as soon as their behavior will permit it. Thus, this problem becomes a societal one, but it is our responsibility as professionals to educate the public and be advocates for resources for comprehensive and early treatment of our patients, treating them as persons with complex problems rather than as containers of malfunctioning machinery.

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## Comments on Task Force Report on Psychiatric Residency

SIR: It was with genuine sadness that I read the recent joint position paper from the Association for Academic Psychiatry and the American Association of Directors of Psychiatry Residency Training entitled "Psychotherapy Training for the Psychiatrist of the Future" (1). Except for the references, the suggested thrust for the future seemed no different from what could have been written 30 years ago.

Although a letter is certainly not the forum to debate the adequacy of any theory of personality or psychotherapy, it is important for psychiatry to realize that these debates exist. To mandate the primacy of the psychodynamic approach and to assert that other views of psychotherapy are subspecialties rather than alternatives is to limit diversity.

Viewing transference and countertransference as central to the understanding of all patient-therapist interactions does as great a disservice to the understanding of other positions as would mandating that the psychodynamic theory of transference be understood only as an example of response generalization. Choosing long-term expressive psychotherapy as paradigmatic and the best way to learn about psychopathology dangerously narrows the choices of future psychiatrists.

Stating that even supportive psychotherapy needs to be psychodynamically informed to be performed adequately ignores the major contributions of Carl Rogers, the client-centered approach, and a different conception of human nature that is not based on conflict. Asserting that psychotherapy must be understood in a developmental perspective distorts the contributions of the rational-emotive and the strategic-systemic positions, as two prominent examples.

There is insufficient space to mention each of the many arguable points in the article, but the points I have made should not be construed as suggesting that the psychodynamic viewpoint is without value or that psychotherapy should not be a prominent aspect in the training of future psychiatrists. A return to the positions that existed over a generation ago does not equip new psychiatrists to compete as psychotherapists with more broadly trained mental health professionals in other disciplines. To view the teaching of other major schools of psychotherapy as obscuring the task and diffusing the effort seems to slight the intellectual capabilities of psychiatric residents and imply that they cannot handle a diversity of views.

An old maxim states, "If your only tool is a hammer, then every problem is a nail." The decision to elevate the psychodynamic approach to a central position could lead psychiatrists in training to obtain a hammer and be forced to compete equipped with a poorly stocked toolbox. A mandate

for the future should be more than just a legacy from the past.

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SIR: The task force on psychotherapy training in psychiatry may be working against its worthy goal by placing individual psychodynamic training in an exalted position while relegating other approaches to the status of subspecialties to be covered in a portion of the last year. Although the experience of working intensely with an individual over a period of time has much to teach, we should recognize that the lessons learned in this forum generalize only partially to other modalities such as group, family, and marital therapy. Have we become trapped by historic contingency in the assumption that study of an individual in therapy is the royal or only road to understanding behavior and becoming a competent therapist? As I see it, psychotherapy is increasingly being done by nonmedical practitioners (many of whom are quite competent) who emerge from programs in which this is not the dominant assumption but in which hypnotic, cognitive, and behavioral techniques are taught in a variety of settings. We can be sure that trainees emerging from psychiatric residencies will be grounded in differential diagnosis and the use of biological treatment; the question for psychiatric education is how to provide models and flexible skills based on what has been learned during the past 100 years about effective nonbiological interventions. From this perspective, several points seem important. 1) Inner personal and interactional experiences combine to affect thought, feeling, and behavior at different levels of relevance with changing situations. 2) We have dynamic models that help us to order the relevance of these factors in the genesis, maintenance, and modification of symptoms. No set of factors need to be relegated to a position of secondary importance, for currently available treatment skills permit us to move between "inner and outer space." 3) These skills relate to being able to form an alliance with more than one person at a time, setting goals and priorities, sequencing tasks in therapy, and remaining aware at each moment of the factors that are in focus. Such skills are certainly as important in the practice of therapy as those which are more traditionally described, such as recognition of defenses and provision of interpretation.

I am always amazed to discover how easy it is, as we struggle to understand and influence behavior, to become stuck on either side of this fence. Years ago, as a child psychiatrist working with a group of family therapists, I noted a tendency in this context to attend to the "system" while ignoring the inner experience of the symptomatic child or depressed parent. I am pleased to see in recent case descriptions that family therapists have rediscovered the individual and emphasize the movement between individual and family. In our training programs we can provide models which give equal prominence to inner and interactional dynamics from the start rather than sending the message that one set of factors is more relevant than the other.

I sometimes wonder how things would have gone if Freud and his followers had decided to focus on dysfunctional marriages (assuming that Victorian marriage would have admitted an outsider) rather than individuals. Then, perhaps, the marital dyad would have been the experience from which our prime model of therapy grew—not inconceivable, and worthy of consideration as we look at our history in order to retain what is most valuable for the future of dynamic, nonbiological therapy.

RICHARD EVANS, M.D.
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SIR: The suggestion by Dr. Mohl and colleagues that supportive psychotherapy should be taught after residents have learned and consolidated core concepts of insight-oriented psychotherapy ignores the structure of residency programs, which require residents to provide supportive psychotherapy before they have had time to learn insight-oriented therapy. I suggest that the nature of the residency requires that effective psychotherapy training begin with issues of what supportive treatment is and how it is provided.

In their first 2 years of training, residents are called on to care for the most fragile patients and to provide supportive interventions (e.g., hospitalization, an alternative ego for reality testing, etc.) in addition to ordering laboratory tests and prescribing medications. The resident and ward staff must help patients strengthen their defenses and contain painful experiences. A curriculum that does not address questions of supportive treatment leaves the resident's inevitable theoretical misconceptions and technical errors unchallenged, and so they are repeated. The resident may not see the enormous benefit patients receive from supportive interventions and may form his or her earliest identity as a psychiatrist solely around dispensing somatic treatments. This early identity may be resistant to change in later years.

In the clinics where residents work, most patients whom these residents see throughout training are in predominantly supportive treatment. If we try to teach residents insight-oriented treatment while they are working with patients needing supportive treatment, the likely outcomes are that 1) residents will feel that psychodynamic theory is outdated or inaccurate (this idea will be reinforced if the teaching is done by part-time clinical faculty instead of by primary role models), and 2) residents will inappropriately apply an insight-oriented approach to patients needing support; the result will be treatment that stagnates, ends prematurely, or makes the patient worse. All of these outcomes interfere with residents' ability to incorporate an understanding of psychodynamics into their identity as psychiatrists and hamper their ability to treat patients.

I believe that it is the resident's primary involvement in supportive treatment and not, as the authors suggested, uncertainty about the future which accounts for the "discrepancy" in recent surveys. Since the vast majority of residents' time is spent doing supportive treatment, psychiatric educators value psychodynamically informed supportive skills and place less value on the specifics of insight-oriented treatment.

I agree with the authors' conclusion that "the psychiatrist of the future must be deeply and effectively psychodynamically informed and have the opportunity to become psychotherapeutically competent." However, I believe that to accomplish this goal, the curriculum must teach psychodynamic theory and technique as it applies to supportive treatment, because that is what residents will be doing. The psychotherapeutic tenet of working with the patient where he is must

also be applied to the education of psychiatric residents. We must teach the residents where they are.

SCOTT N. LURIE, M.D.
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SIR: Although the report of Dr. Mohl and colleagues on psychotherapy training is a thoughtful contribution, I believe it contains two significant flaws.

The first is the authors' assertion that the "best way . . . perhaps the only way, to learn and consolidate . . . [psychodynamic] core concepts and experiences" is through the practice of insight-oriented psychotherapy. This view, in effect, relegates theoretical understanding to a time when the resident will already have substantial experience doing psychotherapy. It also assumes that he or she will have the therapeutic experiences which are necessary for adequately illustrating psychodynamic concepts.

Surely, there can be no important objection to, and every advantage in, teaching these concepts—in an introductory fashion—from the very onset of residency education. Just as theory without practice is a sterile exercise, so practice without a theoretical basis tends to fall into a narrow empiricism.

The second concept of the authors with which I take issue, and which is closely related to the foregoing, is their view that learning about supportive psychotherapy should also be relegated to a time when the resident shall have learned about psychodynamic concepts through doing insight-oriented psychotherapy. If this approach is followed, it means that residents will be unable to practice supportive psychotherapy, when it is indicated, with the inpatients for which they are responsible.

There are further negative implications inherent in the authors' plan. For example, to evaluate patients for insight-oriented psychotherapy, residents need to possess at least some understanding of psychodynamic concepts insofar as they affect one's choice of therapeutic modality. During postgraduate year 3 (PGY-3) the vast majority of outpatients seen in clinic settings require supportive psychotherapy, at least to some extent. Who, if not the residents, will assume the responsibility for treating these patients? For too long the practice of supportive psychotherapy has been assigned to the least knowledgeable and least experienced members of the outpatient team, ignoring the intellectual and emotional demands of such work.

It is my impression that one of the reasons that insight-oriented psychotherapy does not enjoy the reputation it merits is that its teachers and practitioners have too often neglected the great mass of patients who require skilled, psychodynamically informed supportive psychotherapy. This problem is compounded when psychiatrists dichotomize treatments as either biological or psychological. If we are planning the psychotherapy education of residents for the future, I believe we ought to take into primary consideration the needs of the patient population.

The program that Dr. Mohl and coauthors have elaborated is a useful beginning, but I believe that its programmatic priorities will benefit from revision.

DAVID S. WERMAN, M.D.
*Durham, N.C.*

SIR: In a time of emphasis on biology, the Special Article on psychotherapy training for the psychiatrist of the future presented a much-needed reevaluation of the importance of psychodynamic psychotherapy in the training and work of psychiatrists. Although the suggested model curriculum was meticulously explored and presented, I would call attention to one important omission. It is noteworthy that in discussing the clinical care requirements for PGY-3 residents, the authors emphasized that "patients should represent diverse experiences in terms of gender, diagnosis, age, phase of life, developmental level, and cognitive style." However, it is curious that in recognizing the important influence of these variables on psychotherapy, the authors failed to mention culture, despite the growing recognition that culture needs more attention in psychiatric residency training. Overviews of culture and residency training (1, 2) remind us that both the influence of culture on psychiatry and the poor track record of psychiatrists in providing psychotherapy and other services to ethnic and socioeconomic minorities are well documented, and that residents themselves (of any cultural background) seem to have cultural preferences that lead to inequitable treatment.

To address this omission, in reference to the model and minimum curriculum, I suggest that in a model curriculum, a resident should have at least one psychotherapy patient of a different cultural background. In a minimum curriculum, residency directors and supervisors should pay attention to the omnipresence of the cultural variable, since transference and countertransference problems can also arise in treating patients who are culturally similar to the therapist (3).

While perhaps the authors meant to subsume culture under the gender or cognitive style variations, I think that this would be misleading and begging the question. I hope that the omission of culture was an oversight, for if the leading psychiatric educators continue to ignore the importance of culture in the education of residents, our patients will suffer the consequences of our not truly following the biopsychosocial model, and our development as psychiatrists may be compromised.

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SIR: I am enraged to see that personal psychotherapy was not recommended in the curriculum for psychotherapy training. I believe that as the training analysis is the most critical component of analytic training, so too a training psychotherapy should be a critical and mandatory part of a psychotherapy curriculum. The authors stated that a personal psychotherapy "can no longer be a general requirement of residents, who now enter psychiatry for widely varied motives." However, since most psychiatrists do see patients, psychiatric residents should have the experience of being a patient as part of the training process. Moreover, if the mandatory requirement of individual psychotherapy were to deter prospective candidates, I believe that our profession as a whole would benefit. I strongly feel that, if nothing else, the experience of being a patient teaches humility and empathy, which cannot be taught by any other method. As individual supervision is part and parcel of psychiatric training, so should personal

psychotherapy be. As a trainee, I am quite surprised that a task force on psychotherapy training is not supporting my position.

SHIRAH VOLLMER, M.D.
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SIR: The report by Dr. Mohl and other members of the task force on psychotherapy training for future psychiatrists is fallacious. After surveying themselves (1) and discovering what they already knew, they pretended to discuss it objectively in a self-appointed task force and drew conclusions that they then set forth as a universal model for future residency training.

The authors claimed (without proof) that countertransference management and psychodynamically informed supportive therapy are central to the training of all psychiatrists. In support of this basic proposal, they first declared that psychodynamic therapy is "an effective treatment for many mental disorders." There are reasonable data for the effectiveness of cognitive and behavioral therapies, but the jury is still out for psychodynamic therapy; it is certainly not efficacious for "many" disorders. The authors stated further that psychotherapy training is necessary for developing the "complete" psychiatrist. For those of us who think psychodynamic theory extraneous, this appears to be developing the overinclusive psychiatrist. They then proposed that we need such training in order to supervise nonmedical professionals who practice psychotherapy. But, as the latter often do it better than psychiatrists, what is the point? Training in psychotherapy, the authors claimed, provides for more effective consultation to medical colleagues. Do the latter yearn for metaphysical explanations in managing their intensive care, emergency, and surgical patients? Psychotherapy training, the authors declared, enhances learning about other dyadic relationships within psychiatry, as if psychodynamic psychiatrists were better at these than biological psychiatrists. Has someone studied this?

Dr. Mohl and coauthors asserted, moreover, that psychodynamic training "allows observation of complex pathological and normal functioning over time." Is this better than the longitudinal observations of a good descriptive psychiatrist? Finally, we were told that such training enhances the ability to "avoid ethical dilemmas and transgressions." Do more biological psychiatrists than psychodynamic psychiatrists have sex with their patients? Will knowing a theory make you an ethical person?

Having exhausted their rationales for requiring psychodynamic training, the authors presented their plan for implementing it. We were told that trainees in PGY-1 must videotape many open-ended initial and follow-up interviews to be subsequently observed, critiqued, and digested by peers and supervisors. This is to be done while the trainee is simultaneously struggling through medicine and neurology and attempting to learn the ever-changing diagnostic categories of sequential official diagnostic manuals as well as trying to master diagnostic and patient-management procedures. In their PGY-2 through PGY-4 years, residents are then to treat a large number of long-term individual patients weekly or twice weekly, read a host of books, and participate in a variety of seminars. "Resource-poor" programs, the authors suggested, may be unable to implement all of the training procedures as proposed, but agnostic resource-rich programs apparently will be required to offer the entire spectrum of training—or else!

If residents do not know how to make diagnoses and use somatic treatments, they certainly will not be good practitioners, but is there any evidence that familiarity with psychodynamics makes one a better doctor of psychiatry? If I practice good biological psychiatry and my interactions with patients and their families are similar to those of a skilled, caring internist or general practitioner, do I need all the rest of it? The model proposed by Dr. Mohl and colleagues is likely to become accreditation law, even though it is only a belief system. It is unfair that programs that do not share that belief will be forced to comply.

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### Dr. Mohl and Colleagues Reply

SIR: It comes as no surprise that our task force's recommendations stirred comment and controversy, thus reflecting the importance of many of the issues we were addressing. Some of the issues raised by the letters reflect misunderstandings of what we were trying to say. Others reflect substantive points that stirred controversy within the task force itself. We welcome the opportunity to clarify and respond.

Despite our attempts to reduce theory-specific jargon to a minimum, it seems that language we thought applied across various psychodynamic theories can have very different connotations to others. To us, psychodynamic therapy is far broader than any of the specific psychoanalytic theories, yet it includes all of them. It also includes interpersonally oriented approaches and humanistic approaches and even shares some conceptual space with certain recent developments in cognitive theory. All of these theories are based, explicitly or implicitly, on the observation that there are dynamic unconscious processes which powerfully influence human behavior, that these processes are modified and modulated by various developmental and adaptive efforts, and that exploration of the patient's inner and interpersonal experiences and observation of the therapist-patient interaction over extended periods of time reveal these processes and offer opportunities for change. The theories differ in the hypothesized content of these unconscious processes, the primary sources of these processes, and the preferred interventions for changing them. We argued that the best way to appreciate the general nature and power of these processes is to sit with enough patients long enough, intensively enough, and with the appropriate supervisory and didactic support.

Further, our emphasis on individual expressive psychotherapy does not preclude offering additional clinical, supervisory, or didactic experiences in other modalities. Our point here is that in the past, one did not have to provide a carefully thought-out special curriculum to ensure adequate training in expressive psychotherapy. One could assume that in the PGY-1 and PGY-2 there would be strong site-based preparation for a PGY-3 outpatient experience emphasizing expressive psychotherapy. Such assumed internal coherence and emphasis in training programs are no longer inevitable. A self-conscious curriculum is required.

With this as background we would like to address the specific issues raised by the letters.

Dr. Kingsbury assumes, we believe, a far more narrow definition of psychodynamic psychotherapy than we were using. Contemporary dynamic models are not based solely on conflict. He also assumes that our proposal was intended to preclude the concurrent teaching of other theories and techniques. When we spoke of "diffusing the effort," we were referring to the task force's task and were explaining our rationale for not trying to propose a truly comprehensive curriculum that would address family, behavioral, marital, supportive, group, and other therapies together with individual expressive psychotherapy. We agree that Rogerian, rational-emotive, and strategic-systemic perspectives need to be taught and that residents should be helped to integrate these perspectives with other theoretical positions. We do disagree about the importance of a developmental perspective. An appreciation of the cognitive processes of children at various maturational levels of the CNS, and the implications for stage-specific behavioral learning, is an essential content area for all psychiatrists.

Dr. Evans also raises the issue of other theories and modalities but articulates it within a fine description of the general task of psychiatric residencies with regard to psychological interventions. We were not trying to address this general task, only a key component of it. We did not intend to imply that marital, family, or other interactional systems approaches should be eliminated. These too are key components that should be taught.

Dr. Lurie raises the practical issue that teaching residents expressive psychotherapy when most of their site-based patients require supportive psychotherapy may result in the opposite of the attitudinal effect intended, as well as major, persistent technical errors. The tack of teaching supportive and/or brief psychotherapy first is taken by many programs for exactly this reason. That is also why we feel that assignment of appropriate cases, early in training, is a crucial part of our proposed curriculum. All of us have seen too many residents and practicing psychiatrists who are excellent supportive psychotherapists but think they are doing exploratory psychotherapy. We endorse the idea that supportive psychotherapy should be taught from the beginning, especially at the sites where residents usually work in the early years of training, and that it should be studied again late in training when the trainee is much more sophisticated.

Dr. Werman makes a similar point and implies (and we agree) that the support versus insight dichotomy is as pernicious as the biological versus psychodynamic one. We actually advocate learning supportive psychotherapy and exploratory psychotherapy in tandem in a carefully thought-out, coordinated curriculum. Dr. Werman also feels that we have downgraded the importance of theory. We think not, and have emphasized it in the proposed seminars. However, we strongly believe that all the theory in the world is useless in the hands of a resident who has not yet learned to sit with a patient in pain and listen well to both the patient and himself/herself. Therefore, we emphasized experiential learning early in training. Introductory theory seminars that do not detract from this learning would be valuable.

Dr. Moffic's comments are absolutely on target and we can only express our chagrin at the oversight in omitting cultural background as a crucial variable in identifying appropriately diverse patients for residents' PGY-3 psychotherapy experience. We fear that our oversight is an example of the very need for greater attention to cultural issues in psychiatry that Dr. Moffic and others have advocated.

Many model curricula now collect dust on training directors' shelves because they are wholly unrealistic. We were mindful of this in our work. All of us believe that personal psychotherapy is a valuable part of training, but we concluded that it is no longer realistic (on a number of counts) for it to be required. This is why, after much discussion, the task force took a position different from that of Dr. Vollmer.

Dr. Taylor's letter represents a particularly extreme dichotomous viewpoint. We do not equate "biological" with "not psychodynamic." He seems to. We cannot help noting that others who might be identified as primarily biological psychiatrists do not feel the same need for either-or thinking (1). We endorse training for competence in all areas of psychiatry. The data support the effectiveness of all kinds of psychotherapy (2–4) and have done so since 1970; more recent data support the incremental effects of longer courses of therapy (5). We surveyed all programs, presented our ideas for review at two national meetings, had our work under constant review by the executive bodies of both parent organizations, and incorporated much of the feedback. Dr. Taylor attributes to us assertions or implications that we do not believe were in our report (e.g., needs of medical colleagues, ethical distinctions between types of psychiatrists; two PGY-2 cases is not a "large" number; "at least one" PGY-1 taped interview is not "many"). But he does raise some interesting research questions (competency of dynamically versus nondynamically trained psychiatrists in dyadic therapy) that we think are worthy and should be pursued.

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### Integrated Paradigm for Psychiatry

SIR: Hector C. Sabelli, M.D., Ph.D., and Linnea Carlson-Sabelli, R.N., M.S. (1) described a potential integrative paradigm for psychiatry based on mathematical nonlinear dynamics and derived from process theory. We share their excitement at the possibility of grounding psychodynamics and psychotherapy (2), biological psychiatry (3), and social psychology in a unified testable theory. However, their explanations of some of the basic concepts of nonlinear dynamics are somewhat misleading and provide little that is useful to their intended audience. The concepts of bifurcations and chaotic attractors were first equated with one another (p.

1541), then bifurcations were noted to derive from chaos (p. 1548). We do not understand this assertion, as bifurcations occur in the absence of chaos, but not vice versa (4). Without clear examples of how this relates to such processes as creative thought and the genesis of neurotic, psychotic, and dissociative structures, nonlinear dynamics are likely to remain foreign concepts to mental health specialists.

In addition, while attempting to show how process theory is superior to systems theory, the authors seemingly chose to ignore the rich literature coming out of the family therapy movement (5) that deals with cybernetics, general systems theory, and the process of change. A review of cybernetics theory and chaos theory quickly shows many areas of overlap. When attempting to dismiss general systems theory by using nonlinear dynamics and process theories as a paradigm, one cannot ignore recent refinements in general systems theory and vast areas of conceptual overlap.

While a review of process theory and mathematical dynamics provides important groundwork, it may be more productive to emphasize specific applications of nonlinear dynamical processes in psychiatry and outline goals for research.

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## Dr. Sabelli and Ms. Carlson-Sabelli Reply

SIR: Our article was not an attempt to apply mathematical dynamics to psychiatry but the first publication of process theory in a scientific journal. In *Union of Opposites: A Comprehensive Theory of Natural and Human Processes* (1), we developed process theory by integrating process mathematics (2), process physics (3), and process philosophy with psychobiology and psychodynamics and discussed the concepts Doctors Meacham and Proctor question. In brief, we would like to make the following points.

1. There are both chaotic and nonchaotic bifurcations (2).
2. Chaos and bifurcation serve as models for creativity. High energy inputs drive chemical processes far from equilibrium, starting oscillations and chaos and forming novel dissipative structures (3). Similarly, metabolic disequilibria lead to psychotic turmoil and create delusional psychotic structures; neurotic conflicts lead to fragmentation and formation of neurotic structures; severe stress leads to dissociation and formation of dissociative structures (1). Creative children, when confronted with a loving and abusive parent, become dissociated (chaos), forming and switching between (bifurcation) multiple personalities (dissipative structure) as a result of the higher energy created by the tension of opposites; other models postulate decreased energy (Janet), energy displacement (Freud), or developmental deficit (Kohut) (1).

The bipolar individual's high nervous energy exaggerates pathologically his or her tendency to equilibrium (reactive depressions and manias, not feedback deficits) and endogenous rhythms (alternations between opposite moods as periodic attractors). It promotes creativity (manic-depressive artists) and the creation of personality deviations and psychotic delusions (chaos and bifurcation) (1).

3. There are differences from systems theory. Creative processes are far from equilibrium, not homeostatically equilibrated systems. Society creates individuals more complex than itself, not social systems composed of simpler individuals (4). Biological priority, social mediation, and psychological supremacy yield a biosociopsychological model, not a biopsychosocial model (4).
4. Family therapy goes beyond the mechanical models of computer systems and uses process concepts. Process theory derives from dynamics, cybernetics, and other sources. Priority of the simple and supremacy of the complex derives from Jackson's levels of organization of the nervous system. Cosmic asymmetry, proposed by Pasteur, is interpreted as the time arrow of energy and entropy. Female priority and male supremacy is a novel social and psychodynamic thesis derived from the union of opposites. The union of opposites, stemming from Heraclitus, Lao-tzu, Hegel/Marx's dialectics, Bohr's quantum complementarity, and Freud/Jung's psychodynamic oppositions, is interpreted as a tendency for processes to move toward attractors, including equilibrium points (entropic decay), periodic attractors (physical, biological, and psychological rhythms), and creative attractors. The concept of creative attractors is based on Prigogine's thermodynamics of processes far from equilibrium. As a model for psychological and social differentiation, it contrasts with theories of predetermined development. Process theory provides both a psychodynamic and a philosophical interpretation of mathematical dynamics; conversely, it provides clinical psychodynamics and process philosophy with mathematical tools. Our purpose was to develop a theory for the social and psychological human sciences, as an integrative union of opposites: biological and psychological psychiatry, dynamics and psychodynamics, mechanism and dialectics, materialism and idealism, science and humanities.

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## Monitoring Quality Assurance in Psychiatry

SIR: The otherwise excellent article by Michael A. Fauman, Ph.D., M.D., on quality assurance monitoring in psychiatry (1) contained the following erroneous statement on

page 1122: "Health care organizations are required to send the results of quality assurance monitoring to JCAHO on a continuing basis." Dr. Fauman has perhaps confused the *internal* quality improvement program of the Joint Commission on Accreditation of Healthcare Organizations (2) with a goal of JCAHO's agenda for change, which Dr. Fauman also mentioned. JCAHO has appointed a quality improvement task force that will meet throughout 1989–1990 and "will address its efforts to the design of a framework for the use of both clinical and organization and management indicators in the monitoring and evaluation activities of hospitals and other health care organizations" (President's report to the JCAHO Board of Commissioners, Dec. 10, 1988).

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## Thyroid Dysfunction in Postpartum Depression

SIR: I enjoyed the review article by Michael J. Gitlin, M.D., and Robert O. Pasnau, M.D., on psychiatric syndromes linked to reproductive function in women (1). Psychiatrists are often consulted to help in managing the more severe forms of postpartum depression. It is important to recognize that postpartum thyroid dysfunction is an important cause of late postpartum depression and should be screened for in all such patients. My colleagues and I feel that this was an important omission in the article. Consulting psychiatrists should be aware of the importance of a simple thyroid-stimulating hormone (TSH) screen to rule out transient hypothyroidism as the cause of late postpartum depression (2, 3).

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## Dr. Gitlin Replies

SIR: Dr. Claman reminds us that thyroid dysfunction is a possible cause of postpartum depression. We have no quarrel with using a TSH measurement as an appropriate screening test. However, we are not aware of any evidence suggesting that hypothyroidism is a frequent *cause* of postpartum depression (as opposed to the transient, probably nonpathological, alterations in TSH or the free $T_4$ index that may be seen around the time of childbirth).

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## Carbamazepine and SIADH

SIR: Arifulla Khan, M.D., and associates (1) were not entirely correct in stating, "Psychiatric reviews reporting SIADH [syndrome of inappropriate secretion of antidiuretic hormone] induced by psychotropics have not included carbamazepine." A review by Illowsky and Kirch in this journal (2) mentioned carbamazepine first on the list of SIADH-inducing psychiatric drugs. A British psychiatric review (3) also mentioned the association of SIADH and carbamazepine (albeit carbamazepine is classified as an anticonvulsant).

I also wish to point out that Dr. Khan and associates' patient did not continuously meet the criteria they gave for the diagnosis of SIADH. For example, on day 14, the final day of carbamazepine therapy, her serum sodium level was 131 meq/liter, which was not significantly different from her level at admission, 134 meq/liter.

The authors rightly stated that the patient's other psychotropics and her smoking may have contributed to her SIADH. I believe that Dr. Khan and colleagues would be well advised to read the cautious strategy recommended by Sandifer in his review (4), particularly in view of their polypharmacy. In my opinion they did not show beyond doubt that the patient had SIADH or that carbamazepine was responsible.

Sandifer concluded that medication-induced SIADH may be transient and that the medication may possibly be continued, if clinically indicated, by using fluid restriction and, perhaps, demeclocycline, which enhances sodium retention. As nicotine is a potent releaser of ADH, I feel that a smoking ban in all suspected cases is also warranted.

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## Dr. Khan and Associates Reply

SIR: We appreciate Dr. Cooney's comments. He has raised several critical questions that need to be addressed. We agree that polydipsia and water intoxication with robust clinical features have been included in recent psychiatric reviews (references 2 and 3 in his letter). However, our patient did not manifest robust clinical features, including psychogenic polydipsia, changes in the cardiovascular system, or changes in behavior suggesting organic brain syndrome. Only repeated checking of her serum sodium level led to a *laboratory* diagnosis of SIADH.

The multiple drugs (nicotine, imipramine, perphenazine, and carbamazepine) used by this patient with a history of ECT may have lowered the threshold for dysregulation of CNS mechanisms for fluid and electrolyte balances. The patient continued to smoke secretly (she had smoked 30 cigarettes a day for 45 years), but fluid restriction (<1 liter/day) led to improvement in her electrolyte balance, with the result that she no longer met the laboratory criteria for SIADH. The decision to stop carbamazepine on day 14 was made in conjunction with her referring physician and the consulting internist.

The extent of such subclinical but important changes in electrolyte balances in psychiatric patients taking carbamazepine is not well delineated. This is of some importance, since carbamazepine may be prescribed more frequently for patients with refractory and multiple illnesses. The suggestions of Dr. Cooney for managing patients with polydipsia, water intoxication, and SIADH are supported by earlier investigators (references 2–4 in his letter).

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## Comments on Antidepressant Response to Sleep Deprivation

SIR: Joseph C. Wu, M.D., and William E. Bunney, M.D., presented a thorough and thought-provoking discussion of the antidepressant response to sleep deprivation in their review (1). They referred to two studies conducted in our laboratory (2, 3); although these were accurately reported, the studies are now somewhat out of date and to some extent misrepresent our current thinking about sleep deprivation.

We agree that among a certain subgroup of depressive patients, a process associated with sleep is depressogenic. First, our own experience (largely with treatment-resistant depressive patients) is that with very rare exceptions, a full relapse accompanies the return to sleep after successful sleep deprivation, regardless of medication status. Second, in our nap studies we have found that after successful sleep deprivation, relapse could be precipitated by very brief periods of sleep, and at varying times of the day, in a patient who had previously been euthymic under conditions where no sleep was permitted (2–4). In addition, we have demonstrated that the improvement in response to sleep deprivation can be extended by delaying the "recovery" sleep that ends the procedure, but relapse then ensues with a return to sleep (4). Finally, we have shown that a patient who relapsed during apparent behavioral wakefulness was subsequently found to have slept for several minutes, accumulated over many very brief sleep periods, when the results of the ambulatory EEG recording were examined (5).

We further agree that the depressogenic effect of sleep is state dependent (6). In our opinion the best evidence for this theory is that although it can be clearly demonstrated in a single depressed subject that sleep has a depressogenic effect (2, 4), this effect is no longer present when the patient is in remission. However, whereas Drs. Wu and Bunney suggest that sleep is directly depressogenic—perhaps through the release of some substance at sleep onset—we believe it is more likely that sleep occurring in interaction with some state-dependent, permissive physiological environment leads to depression. Further, since full relapse can be precipitated by such very brief periods of sleep, and in the absence of evidence of REM sleep, we have suggested that relapse is perhaps unrelated to the infrastructure of sleep. Rather, we feel that sleep in its function of modulating certain circadian rhythms may be the causative factor (S. Southmayd et al., manuscript submitted for publication).

We wish to make one further point. In sleep deprivation studies of relapse after sleep, it is impossible to disentangle the effects of sleep onset from effects that may be related to the process of awakening. Subjects must, of course, be awakened in order to assess their clinical state. However, in normal individuals, the subjective impression is that the transition to wakefulness is often much more dramatic than the transition to sleep. Drs. Wu and Bunney have searched the literature for evidence of physiological effects associated with sleep onset. We suggest that the process of awakening has been relatively neglected by sleep researchers and merits attention with regard to depressive illness, as well as in its own right.

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SIR: In their review of the antidepressant effects of sleep deprivation, Drs. Wu and Bunney provided cogent evidence for a depressogenic process associated with sleep, and in particular with REM sleep. It is notable that in their review of theories concerning the depressogenic effect of sleep, no mention was made of a psychodynamic theory. In the interest of maintaining a balanced perspective on psychiatric theory, I would like to offer such a hypothesis.

Freud believed that depression is a result of repression of instinctual drives. The need for repression arises when the integrity of the ego is threatened and when more mature defense mechanisms are either inadequate or poorly developed.

During sleep, unconscious elements that are repressed or otherwise prevented from reaching consciousness during waking hours arise. Because of the amnestic barrier that normally exists between sleeping and waking cognition, these elements seldom reach waking consciousness. If the dreamer awakens from a dreaming state, however, the dream process that has just occurred is consolidated into waking consciousness, thereby threatening the integrity of the waking ego. This weakening of the ego, together with the renewed need for active repression, results in depression of mood. The occurrence of maximal depression of mood just after awakening, with gradual improvement over the course of the day, is

consistent with such a time-dependent process of forgetting and repression.

This hypothesis is consistent with data associating REM sleep duration and intensity with depression, and it also predicts a relation between proximity of REM sleep to periods of wakefulness and depression. Such a relation might be expected in depressed patients, in view of their frequent awakenings and reduced REM latency. This theory also appears to explain the phenomenon of depression after a brief nap better than any of the biological theories, which do not include mechanisms involving the time relation between dreaming and awakening but, rather, propose humoral substances that are produced continuously during sleep or selectively during REM sleep.

The endogenous or biological element that predisposes certain individuals to depression is, according to this model, the sleep/wake pattern characteristic of these patients. Thus, the reduction of REM periods by antidepressants would have a psychodynamic antidepressant effect independent of any direct effect on neurotransmitter levels during waking hours. Exogenous depression may be relatively refractory to treatment with antidepressants, since its psychodynamic mechanism involves a relative dysfunction of the waking mechanisms of ego defense, and it is not expected to respond as well to sleep deprivation.

A psychodynamic theory of sleep-related depression seems to explain more of the data than humoral theories, while at the same time suggesting other humoral mechanisms for the observed effect relating to known neurotransmitters, such as serotonin, which are involved in regulation of the tempo and pace of the sleep/wake cycle. Psychodynamic theories can and should be developed hand in hand with biological theories, so that these two aspects of psychiatry may be mutually consistent and complementary, rather than disparate and contradictory.

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### Drs. Wu and Bunney Reply

SIR: Drs. Southmayd and David suggest that sleep may interact with some state-dependent, permissive physiological environment to produce depression. Their proposal is not incompatible with our theory. We noted in our article that sleep as a depressogenic process would be only one of many factors that are involved in the complex CNS control of depression. We also noted in our article that the antidepressant effects of sleep deprivation may be state dependent, since some normal persons who are sleep-deprived report dysphoria rather than mood elevation.

Drs. Southmayd and David also suggest that the process of awakening merits attention. This is an interesting idea, but as they point out, it may be impossible to disentangle the effects of awakening from the effects of sleep onset. Drs. Southmayd and David also note that their articles which we cited were out of date and misrepresent their current thinking. However, the articles that they cite as representing their current thinking were in press and not available for our review.

Dr. Germine has raised an interesting perspective with his desire to develop a psychodynamic theory of sleep's depressogenic effects. However, evidence cited in our article indicates that slow wave sleep without REM sleep can have a profound depressogenic effect. This observation would seem to be incompatible with the psychodynamic theory proposed by Dr. Germine. We are investigating the effects of psychodynamic measures during REM sleep with positron emission tomography and have found interesting results, which are being prepared for publication.

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### Late-Life Onset of Panic Disorder

SIR: We read with interest the article by Daniel J. Luchins, M.D., and Robert P. Rose, M.D., Ph.D., entitled "Late-Life Onset of Panic Disorder With Agoraphobia in Three Patients" (1). As these authors mentioned in their report, the initial onset of panic disorder in elderly patients is presumably rare (2). However, the cases they described confirm our prior observations of patients whose panic attacks began after the age of 60. The purpose of this letter is to report additional cases verifying the existence of late-life onset of panic disorder.

We reviewed the cases of all patients over 60 years of age meeting the *DSM-III-R* criteria for panic disorder who had been seen within a 3-year period in the geriatric psychiatry and anxiety disorders sections of our institution. Charts were reviewed by the two of us, and all of these patients who had no history of panic attacks before age 60 were classified as having late-life onset of panic disorder.

Ten patients reported initial onset of panic after age 60. Eight of these 10 patients were women. Their average age was 66 years (range=62–81). All of these patients except one had concomitant medical illnesses, although in all cases the illnesses had been stabilized with appropriate treatment. Six patients had accompanying agoraphobia, and eight had clinically significant depression. All of the patients showed moderate to excellent response to medication, to psychosocial intervention, or to a combination of both treatments.

Our findings provide additional evidence that panic attacks and related psychiatric disorders do, in some cases, emerge for the first time in later life. The popular conception of panic disorder as a problem of early adulthood may simply be another reflection of how little is currently known about anxiety disorders in the elderly. The clinical presentation of late-life onset of panic disorder raises a number of questions that should be addressed by more systematic research. It is important to determine whether panic disorder that begins later in life is in some way clinically distinct from the prototypical panic disorder experienced by younger adults. Even if symptom profiles of the two panic syndromes are found to be similar, their sequelae may be quite different. For example, given that older individuals typically experience a greater number of physical limitations, it is possible that agoraphobia develops more rapidly following late-life onset of panic disorder. It is also of considerable importance to identify factors that might explain why, in certain individuals, panic onset is delayed until later life.

Ultimately, we hope that our data and those reported by Drs. Luchins and Rose will focus more attention on the diagnosis of anxiety disorders in the elderly and stimulate much-needed research relative to the development of safe and effective treatments for anxiety disorders in this age group. Although our sample generally responded to treatment, systematic research is also needed to determine whether the effective interventions currently available for panic disorder are applicable to older individuals.

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### Success of Alcoholics Anonymous

SIR: I wish to thank Marc Galanter, M.D., and associates for their research in an effort to understand the success of Alcoholics Anonymous (1). I believe their results can be explained by the psychoanalytically derived concepts of self psychology discovered by Heinz Kohut (2, 3). The psychodynamic concepts include mirroring, idealizing, and twinship selfobject needs, their respective transferences, and transmuting internalization leading to development of autonomous self function. A fragmented, enfeebled, unharmonious self looking for soothing and esteem through alcohol and other drugs can become cohesive, vigorous, and harmonious without drugs when important missing selfobject functions are provided in treatment. I believe this includes any treatment, in any setting, for almost any diagnosis in *DSM-III-R* and stands in contrast to what Dr. Galanter and associates describe as the "clinical and more detached ambience of most psychiatric facilities."

It is also strongly implied in their article that it takes at least a year or two of intensive treatment for self functions to become integrated. This adds support to my belief that brief psychotherapies have serious limitations in providing appropriate treatment for many disorders.

Perhaps ways of achieving an effective integration of self-help and psychiatric care can begin by defining a conceptual bridge so essential for the successful outcome of both treatment modalities.

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### Dr. Galanter and Associates Reply

SIR: It can indeed be useful to apply psychoanalytic concepts to the therapeutic processes undertaken in a treatment program such as the one we outlined. We do not feel that there is an incompatibility between these concepts and those with a social-psychological orientation, such as the ones we have used.

Dr. Hoffman appears to suggest that treatment for addictive disorders may take place "in any setting." We feel, however, that certain unique programmatic ingredients, such as the incorporation of a self-help treatment modality like Alcoholics Anonymous, can provide a therapeutic base which will substantially enhance the efficacy of traditional institutional care. In effect, we agree with the respondents in our study who were treated in this setting that Alcoholics Anonymous was of major importance in their progress toward recovery.

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### Borderline Patients' View of Their Parents

SIR: The recent study by Joel Paris, M.D., and Hallie Frank, Ph.D. (1) replicates a previous study we reported (2). Like these authors, we used the Parental Bonding Instrument to study hospitalized patients who had been diagnosed as having borderline personality disorder through clinical interview. We also used two comparison groups. Our results supported the idea that borderline patients feel that their parents are less caring, but we also found that our borderline patients recalled their parents as more overprotective.

Furthermore, the Diagnostic Interview for Borderline Patients is a semistructured interview, as the title suggests (3). Drs. Paris and Frank did not discuss their unorthodox use of this instrument, i.e., in a retrospective chart review.

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### Dr. Paris and Dr. Frank Reply

SIR: We are grateful to Dr. Wise and his associates for bringing our attention to their earlier publication, of which we were not aware. We have in fact repeated our study on a much larger sample, and the results support their finding that borderline patients remember their parents as overprotective as well as neglectful (manuscript submitted for publication).

The retrospective version of the Diagnostic Interview for Borderline Patients (DIB) is an instrument adapted for chart review that uses 29 "summary statements" from the original DIB (1). Armelius et al. (2) have shown that it correlates highly with the original interview.

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## Further Thoughts on Self-Mutilation Following Trauma

SIR: Self-mutilation following trauma such as rape or a combat-related experience has recently been reported by Gail S. Greenspan, M.D., and Steven E. Samuel, Ph.D. (1) and by Roger K. Pitman, M.D. (2). Both reports described self-mutilation consisting of superficial lacerations, primarily of the upper extremities. This behavior is noteworthy for two reasons: 1) it has not previously been reported in connection with posttraumatic stress disorder (PTSD), and 2) it bears some resemblance to the self-cutting behavior seen in borderline personality disorder. Valuable insights on such behavior may be obtained by viewing it within the context of self psychology.

In the cases described in these two reports, several common factors that exert influence on the self-cutting behavior can be seen. First, the behavior appears to be a way of releasing tension. Some of this tension is clearly related to feelings of narcissistic rage that build up in response to the trauma. It cannot be doubted that both rape and life-threatening experiences in combat represent intense narcissistic injuries. The second factor is related to feelings of depersonalization that result from the trauma. Patients in both reports described the self-mutilation as reaffirming their sense of reality. In one of the cases described by Drs. Greenspan and Samuel, the patient always stopped the cutting as soon as she saw blood. This can be understood as visual reassurance that the self was intact.

Kohut described the self as reacting to empathic failures by experiencing intense disintegration anxiety, a signal of impending fragmentation of the self (3). Intense trauma may also lead to fragmentation of the self. Disintegration anxiety is characterized by an intense fear that the self will cease to exist, as well as by feelings that the person is literally falling apart. Depersonalization episodes may be understood as manifestations of the disintegration anxiety. In response to this experience, disintegration products are used to temporarily restore cohesion to the traumatized self (4). The disintegration products described by Kohut included certain perversions, delinquencies, and addictions. I have described the occurrence of violence directed toward others as a disintegration product in PTSD (5). Violence directed against the self in the form of self-mutilation represents a similar process.

Self-mutilation following an intense trauma sufficient to result in PTSD serves the function of confirming the reality and vitality of the damaged self. It offsets fears of fragmentation by proving to the person that he or she is alive. Self-mutilation further serves to release narcissistic rage and other feelings related to the trauma. Finally, the act of cutting oneself provides a temporary stimulus around which the self may regain cohesion to offset the feelings of fragmentation and disintegration anxiety. This is probably the primary function of self-mutilation in both borderline patients and those with PTSD. Thus, self psychology can provide a useful explanation for this behavior by viewing self-mutilation as a disintegration product of the self.

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## Drs. Greenspan and Samuel and Dr. Pitman Reply

SIR: We appreciate Dr. Feldmann's comments on the insights that a self psychology approach can offer to the understanding of self-cutting. While formulating psychological explanations was not our intent in our primarily descriptive case report, we recognize that the self psychology school provides one valuable framework for understanding this behavior.

Freud, in his 1923 paper "The Ego and the Id" (1), stated, "A person's own body, and above all its surface, is a place from which both external and internal perceptions may spring. . . . The ego is first and foremost a bodily ego." Self-cutting may be viewed from this perspective as a pathological process in which there is simultaneous expression of intolerable aggressive strivings and reconsolidation of bodily integrity.

Contemporary research by van der Kolk et al. (2), Fink (3), Putnam et al. (4), and Sandman et al. (5) illustrates additional useful perspectives on the many psychological, behavioral, and biological responses that result from overwhelming traumatic experiences.

We caution ourselves and our colleagues not to apply general concepts to any specific case without a thorough analysis of all aspects of each patient. It is overly simplistic to assume that one set of theoretical constructs can be applied to all patients who have one particular symptom.

We have received similar personal communications from others and we are currently working on a more substantive paper on this topic. Any additional contributions from readers are most welcome.

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GAIL GREENSPAN, M.D.
STEVEN E. SAMUEL, PH.D.
*Philadelphia, Pa.*

SIR: Our society apparently has a need to deny the devastating effects of war, as exemplified by the invincible GI Joe and the immortal Daffy Duck, who can receive a point-blank shotgun blast and escape with only his feathers singed. This denial has not lacked adherents within our own discipline. However, recent findings (1) of a 31% lifetime incidence of posttraumatic stress disorder in male Vietnam combat theater veterans (considerably higher in veterans with high combat exposure) and of increased rates of certain other mental disorders, including obsessive-compulsive disorder, provide definitive psychiatric refutation of the Warner Brothers version of combat. The recognition (or, more accurately, re-recognition) that extreme psychological trauma (2) has dire mental health consequences has amounted to nothing less than a major movement within American psychiatry.

Dr. Feldmann's contribution further clarifies how exposure to flying bullets can injure the mind even when those bullets do not strike the body. Lacking expertise in psychoanalytic self psychology, I do not feel qualified to comment on his characterization of self-mutilation as a "disintegration product of the self." With regard to the self-mutilating combat veteran on whom I previously reported (3), I do know that having to stuff the physical disintegration products of his comrades into rubber bags resulted in feelings of depersonalization that have plagued him ever since. I see this depersonalization as a central element in his compulsive psychopathology and plan to expand on this theme in a forthcoming detailed report of his case.

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ROGER K. PITMAN, M.D.
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## Debate on Late Luteal Phase Dysphoric Disorder

SIR: We are writing in response to the article "Late Luteal Phase Dysphoric Disorder and *DSM-III-R*" by Robert L. Spitzer, M.D., and colleagues (1). The article had two omissions that are important and deserve correction.

The first omission concerns the scope and content of the debate. The article discussed two main objections to the diagnosis under the headings "Nosological Issues" and "Social Issues." This characterization is misleading about the scope of the debate because it neglects the central objection, which was scientific in content. For example, in the debate "Controversies in the Revision of *DSM-III*" that took place at the APA annual meeting in May 1986, our first statement provided the central thesis: "The *research* does not support this diagnosis, and the *lack of scientific evidence* is reason enough to reject it" (2, emphasis added). A summary handout that accompanied the debate was entitled "Research Evidence Does Not Support the PMDD Diagnosis (Premenstrual Dysphoric Disorder)." The two main headings of the handout corresponded to the two scientific objections we raised in the debate, i.e., the problems of correlation without causation and of symptom elevation (the former referring to the apparent link in timing between dysphoric symptoms and the menstrual cycle, which is correlational and does not establish a causal relationship and the latter referring to the fact that self-ratings of cyclicity are sometimes enhanced by awareness of the menstrual cycle focus of the investigation). We are puzzled by this omission, since the article repeatedly referred to a "debate," and at least three of the four coauthors participated in the major debate at the APA annual meeting that we have cited (this is the only such debate that was held, to our knowledge).

Our position was subsequently presented at a conference in New York in October 1987 (Dr. Spitzer participated in the meeting), where our paper was entitled "LLPDD: Substantive, Methodological, and Conceptual Issues." Finally, in the summary publication of our position (3), which was available upon request, a major heading is "Research Aspects."

The second omission specifically concerns the authors' failure to provide primary sources on the debate for those who might wish to consult them. As a leading neuroscientist has said, "An integral part of the system of science is the continuity of the literature, so that any scientist can discover the background of a field by careful reading. Thus every scientist has an ethical responsibility to cite appropriately the antecedents to the present work" (4). It is customary practice to cite public presentations as well as manuscripts. The problem with selective citation is that it impedes the evolution of knowledge and the ongoing processes of scientific debate. We are surprised and saddened that this has occurred here. Elsewhere, one of us has examined the impact of selective citation on the history of science (5).

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JEAN A. HAMILTON, M.D.
SHERYLE J. GALLANT, PH.D.
*Washington, D.C.*

## Dr. Spitzer and Associates Reply

SIR: Although we were hardly neutral about the possible inclusion of late luteal phase dysphoric disorder in *DSM-III-*

R, in our article we did attempt to provide a fair presentation of the many scientific and social issues involved in the controversy. Drs. Hamilton and Gallant take us to task on two accounts: our "omission" of the central scientific issues and our failure to cite two of their unpublished presentations at a debate at the 1986 APA annual meeting and at a subsequent conference in New York in 1987. We regret not including these presentations in our reference list; this would not have occurred had we realized that copies of the presentations were available to interested readers.

In rereading our article we believe that we did address the two central scientific issues that Drs. Hamilton and Gallant raise in their letter. We did this under the heading of "Nosologic Issues," which could just as well have been "Scientific and Nosologic Issues." Our discussion of each of the seven nosologic and scientific issues that we addressed began with an objection to the validity of the disorder in the form of a question.

The issue of correlation without causation was discussed following the question "Doesn't 'late luteal phase dysphoric disorder' imply . . . that something is biologically wrong with the menstrual cycle?" Here we dealt with the argument that late luteal phase dysphoric disorder may be a disorder not *of* the menstrual cycle but *associated* with it. We noted that like almost all of the other names of *DSM-III-R* disorders, this name is descriptive and does not imply any particular theory about etiology. We indicated our wish that all potentially fruitful approaches to etiology be explored, including the role of psychological and social factors.

The issue of symptom elevation being affected by scrutiny of the menstrual cycle was discussed following the question "Since there is no objective measure for the LLPDD diagnostic criterion of functional impairment, how valid can the diagnosis be?" Here we dealt with the argument that the defining symptoms of the disorder rely on subjective statements of the patient which, in the absence of other confirming data, have no objective basis. As we noted, the same problem exists for other diagnoses. Many questions to a patient about possible mood symptoms may enhance the likelihood that the patient will report such symptoms—this does not invalidate the diagnosis of mood disorders.

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SALLY K. SEVERINO, M.D.
JANET B.W. WILLIAMS, D.S.W.
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*New York, N.Y.*

## Criteria for Self-Defeating Personality Disorder

SIR: In their field study of diagnostic criteria for self-defeating personality disorder (1), Robert L. Spitzer, M.D., and colleagues reported that the "total predictive value" (the fraction of patients diagnosed correctly) was maximized at 83% when patients were required to meet at least five criteria to receive the diagnosis. While this statement is correct if the prior probability or prevalence of the disorder is 50% (as resulted from the authors' data collection procedure), it is incorrect at other prevalences. For example, at a prevalence of 14%, using five or more criteria yields correct diagnoses 76% of the time (2); requiring seven or more improves on this (predictive value=86%) but offers no improvement over simply diagnosing all patients as not having the disorder. At low prevalences, total predictive value is a misleading descriptor of diagnostic accuracy (3).

We have suggested that information theory be used to select optimal cutoffs for diagnostic systems (4). This method quantifies the reduction in uncertainty achieved by applying a diagnostic technique to a population in which the prevalence of a condition is known. When we applied the method to Dr. Spitzer and colleagues' table 2 data, we achieved a reassuring result: at all prevalences below 80%, the greatest reduction in uncertainty is achieved by using the five-criteria cutoff (calculations available on request).

One can also make information calculations for each individual criterion for self-defeating personality disorder by using Dr. Spitzer and colleagues' table 1. Again assuming a 14% prevalence, information yield ranges from 0.07 bits for criterion 1 (chooses failure) to 0.03 bits for criterion 4 (incites anger, feels humiliated). This suggests that diagnostic precision would be improved by a weighting algorithm (e.g., a point system) that assigns more importance to some criteria and less to others. The superiority of the algorithm could be tested by using methods described by Murphy et al. (5) and Hanley and McNeil (6); the information-maximizing cutoffs for the algorithm could be established by using receiver operating characteristic methods similar to those we recommended for optimizing the dexamethasone suppression test (4).

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DOUGLAS MOSSMAN, M.D.
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## Dr. Spitzer and Mr. Davies Reply

SIR: We thank Drs. Mossman and Somoza for their comments on the data analysis that we used to determine the number of criteria for the diagnosis of self-defeating personality disorder. The total predictive value is maximized when case subjects and control subjects are equal in number, as in our study. More generally, we believe it appropriate to select the threshold that is characterized by approximately equal sensitivity and specificity, since these values are independent of the prevalence of the disorder in the population. This strategy is based on the assumption, others things being equal, that one is as concerned with minimizing false positives (keeping sensitivity high) as false negatives (keeping specificity high). We believe this is a reasonable assumption

in psychiatry, where the potential dangers of false positives (stigma, giving inappropriate or harmful treatments) seem, across disorders, to equal the potential dangers of false negatives (not giving appropriate treatment).

Had we used this strategy of minimizing the discrepancy between sensitivity and specificity rather than maximizing total predictive value, we would have chosen six rather than five items. This would have resulted in less sensitivity (77% rather than 91%) but greater specificity (84% rather than 74%). Given the considerable concern about the misdiagnosis of self-defeating personality disorder and the surprisingly high prevalence of the disorder that has been found in several studies (1, 2, and unpublished data of R.L. Spitzer et al.), this higher threshold, in retrospect, might be more appropriate than the threshold of five items that we recommended. In fact, we recommend that future studies of the disorder also report the findings when the six-item threshold is used.

We believe that there are two reasons for avoiding the suggestion of Drs. Mossman and Somoza that differential weights be given to the different criteria. First, the use of the diagnostic criteria is made much more complicated if the clinician has to add fractions rather than simply count the number of criteria that are met. Second, and more important, if there are a reasonable number of positively correlated items, as is the case with the diagnostic criteria for self-defeating personality disorder, psychometric wisdom indicates that differential weighting has only a trivial effect on increasing the association with external variables (validity) (3, 4).

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ROBERT L. SPITZER, M.D.
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**Simple Schizophrenia Not So Simple**

SIR: Donald W. Black, M.D., and Todd J. Boffeli, M.D., are to be commended for their effort toward reviving the concept of simple schizophrenia (1). As they noted, poor reliability and doubtful descriptive validity led to the deletion of this diagnosis from *DSM-III*. Is this a valid criticism? Evidence indicates the contrary. It is rather remarkable that only one worthwhile clinical investigation was reported between 1930 and 1968, and the fate of simple schizophrenia was decided. As emphasized by Bleuler (2), schizophrenia simplex is characterized by essential rather than accessory symptoms of schizophrenia. According to Bleuler, fundamental symptoms are present in every case and at every period during the course of schizophrenia; hence, they may also be called essential symptoms. He clearly included catatonic symptoms under the category of accessory symptoms. It is equally clear that *DSM-III* and *DSM-III-R* as well as *DSM-II* have included more accessory than fundamental symptoms. The modern generation of trainees is not exposed to the knowledge of fundamental symptoms except occasionally in oral examinations.

Another important problem is careful history taking. Drs. Black and Boffeli cited the International Pilot Study of Schizophrenia (3), which reportedly "failed to substantiate the usefulness of the classic subtypes of schizophrenia, including the simple subtype." It is noteworthy to recall that the main interviewing tool was the Present State Examination (PSE), which did not adequately 1) include the fundamental symptoms of schizophrenia and 2) cover the longitudinal history; in fact, the PSE history covers a period of 1 month before the day of examination. Thus, the findings of the International Pilot Study with respect to simple schizophrenia are not surprising.

Bleuler (2) described six subtypes of simple schizophrenia. The alcoholic subtype is mostly misjudged, since the patients surrender to drink and the basic disease is overlooked. The litigant subtype is characterized by paranoid behavior, but without delusion. Patients with the eccentric subtype stand out as world saviors, reformers, philosophers, writers, or artists. Tyrannical behavior and disagreeableness without paranoid or catatonic symptoms are specific features of the irritable subtype. Patients with the mild subtype do not have sufficiently pronounced symptoms, whereas irritable, odd, moody, withdrawn, and exaggeratedly punctual behavior characterizes the latent subtype.

While I admire the authors for at least trying to reintroduce the concept of simple schizophrenia, I oppose the use of operational criteria at present. Let us not pretend that we know more about schizophrenia, and particularly the simple subtype, than Bleuler did. I suggest that we first follow the Bleulerian concept of simple schizophrenia and gather data. Some difficulty in acquainting ourselves with the fundamental symptoms of schizophrenia and initial disappointments in research must, however, be anticipated. As preparation, I believe it would serve us well if in clinical case conferences educators would demonstrate and discuss the fundamental symptoms of schizophrenia as well as the accessory symptoms; the latter are obviously easier to elicit. While renewed interest in the negative symptoms of schizophrenia (4) has sensitized us to observing these symptoms, they by no means cover the whole spectrum of fundamental symptoms as described by Bleuler. Perhaps Bleuler should not have termed it "simple schizophrenia," since researchers have not found it to be as simple as the prefix might suggest, although that was not Bleuler's intent.

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RUDRA PRAKASH, M.D.
*Nashville, Tenn.*

### Dr. Black Replies

SIR: Dr. Prakash raises some interesting points about the usefulness of the diagnosis of simple schizophrenia and the relevance of fundamental symptoms to the diagnosis of schizophrenia. He basically raises two issues, which I will respond to individually.

First, Dr. Prakash opposes the development of operational criteria for the diagnosis of simple schizophrenia. He says, "Let us not pretend that we know more about schizophrenia, and particularly the simple subtype, than Bleuler did." Clearly, we were not proposing that we know more than Bleuler, but as our literature review demonstrated, there has never been a consistent interpretation of Bleuler's diagnosis, which more or less invalidates any research on simple schizophrenia. As Dr. Boffeli and I have demonstrated elsewhere (1), even at our institution, in a department known for careful diagnosis and description, the diagnosis of simple schizophrenia was applied to a mixed group of patients. Of 52 patients who received the diagnosis of simple schizophrenia between 1935 and 1950 and were reevaluated according to the *DSM-III-R* criteria, five met the criteria for chronic schizophrenia, 23 for major depressive disorder, two for delusional disorder, and one each for bipolar disorder, obsessive-compulsive disorder, hypochondriasis, pedophilia, organic personality disorder, and depersonalization disorder. Sixteen patients met the criteria for an axis II diagnosis only. What this simple chart study demonstrates is the heterogeneity of the simple schizophrenia diagnosis over the years. We believe that in order to study this concept adequately, operational criteria must be used to improve reliability so that validity can then be assessed.

Second, Dr. Prakash correctly observes that the current generation of trainees is underexposed to Bleulerian concepts of fundamental symptoms. Much of this is probably due to the perceived unreliability of assessing avolition, apathy, social isolation, etc. Accessory symptoms, on the other hand, are relatively easy to describe and elicit from patients during interviews. As Andreasen (2) and coworkers have demonstrated, fundamental symptoms can be reliably identified, and in the future perhaps more emphasis can be placed on these important negative symptoms in the diagnosis of schizophrenia. Bleuler would have wanted it that way.

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DONALD W. BLACK, M.D.
*Iowa City, Iowa*

### Review of Fugitives of Incest

SIR: Judith L. Herman, M.D., in her review of our book *Fugitives of Incest: A Perspective From Psychoanalysis and Groups* (1), did not mention the content of our various chapters. Instead, she judged our publication as a unit. She stated, "Reporting of innovative treatment methods [for incest victims] is sorely needed," but she did not characterize our approach as new or—according to our description—as a "long-term, psychoanalytically oriented group psychotherapy" done by female and male cotherapists (1, p. xi). Rather, she discredited all those features. She wrote that we treated patients "for several years" but failed to report what we "actually did." The psychoanalytic concepts "masked" our observations "by a thick layer of metapsychological language that makes it impossible to replicate their work." ("Metapsychological" refers to Freud's more complex theoretical formulations; the term is used by the reviewer to present our writing as unintelligible.) Finally, a cotherapy pair consisting of "a senior male psychiatrist and a more junior female psychologist . . . seem oblivious to the impact such a model might have on sexually victimized women." Dr. Herman ignored the fact that there are five entries on "power" in our subject index (p. 121) and that we discussed transference distortions leading patients to perceive us as a father/daughter incestuous couple (p. 28).

Questions about outcome are introduced to evaluate our work despite our statement that "evaluating outcome is not the purpose of this book" (1, p. xiii). Comprehensiveness is used as another criterion. Here Dr. Herman found our observations on countertransference of some interest but, in her view, they did not amount to much, since "more comprehensive books [including her own!] . . . address these issues," which is not true.

Prejudice based on sexism and lack of familiarity with psychoanalysis made this review far from objective. The *Journal* should offer its readers—and us—a different, fair, and informative critique of *Fugitives of Incest.*

REFERENCE

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RAMON GANZARAIN, M.D.
BONNIE J. BUCHELE, PH.D.
*Topeka, Kan.*

### Dr. Herman Replies

SIR: Incest is the historic blind spot of psychoanalysis. For close to a century, psychoanalytic tradition ascribed women's complaints of incestuous abuse to fantasy or desire.

The past 15 years have witnessed major advances in the understanding of incest, advances based on a tradition of reporting verifiable data. Psychoanalysis contributed virtually nothing to this explosion of knowledge.

Given this history, one might expect psychoanalytic authors to be receptive to criticism as they belatedly try to catch up with the field. Given this history, one might expect psychoanalytic authors to think twice before accusing others in the field of sexism or ignorance.

I stand by my review.

JUDITH L. HERMAN, M.D.
*Cambridge, Mass.*

### Freud's Major Case Histories

SIR: My concern is the article "Fifty Years After Freud: Dora, the Rat Man, and the Wolf-Man" by Peter Buckley, M.B., Ch.B. (1). I shall limit my remarks to the Rat Man and the Wolf-Man, for they were the subjects of two of my books (2, 3). Each book was based on 3 years of research on the

pertinent psychodynamic, historical, and textual data and commentary to be found in English, German, and French primary as well as secondary sources; I critically synthesized that material and made observations of my own throughout.

In my book on the Rat Man, I included my archival discovery that the patient was actually Dr. Ernst Lanzer. Although he used this name, Dr. Buckley never cited my book in any context; but that is a minor matter. In *Freud and the Rat Man* I devoted some 40 pages to the patient's psychodynamics alone and some 50 to Freud's technique in the treatment. Among other things, I showed how the Rat Man's anal eroticism and particular defensive reactions shaped his free associations and how countertransferential disturbances affected Freud both in his clinical interventions and in the very way he wrote up the case history. Another thing: Dr. Buckley referred to and quoted from his primary document, Freud's case history, without any mention of the reliability of its truthfulness. My book pointed out Freud's intentional confabulation and documented the serious discrepancies between Freud's day-to-day process notes of the treatment and his published case history of it.

With respect to the Wolf-Man, I again limit myself to noting a few among many possible points.

1. In his psychodynamic account, Dr. Buckley related that the Wolf-Man was in treatment with Freud for a 4-year period, then afterward for another 4 months with Freud, and then in 1926 with Ruth Mack Brunswick. What Dr. Buckley did not say in his psychodynamic account is that the Wolf-Man was subsequently—for a half-century (1929 to his death in 1979)—in and out of therapy! This omission is all the more glaring because Dr. Buckley's one reference to my book is for something that is peripheral to its many central theses and findings.

2. Dr. Buckley stated that Freud published his case history "with the frank polemical intent of refuting their [Jung's and Adler's] claims and providing convincing proof of his own." But I have demonstrated (1, p. 116) that Freud's frankness was nothing of the kind; in his text Freud contradicted himself, now saying it was objectively written, now saying that it had a controversial intent—a contradiction which, I pointed out, Strachey silently deleted in his English translation for the Standard Edition of Freud's works.

3. Dr. Buckley rightly named as the *pièce de résistance* in the case history Freud's analysis of a dream that the patient had at the age of 4 years. In his most elaborated explanation of the dream, Freud traced it back to a primal scene putatively observed by the Wolf-Man when he was 1½ years old. The reality of that event, for Dr. Buckley, "remains controversial." *Pace* Dr. Buckley; I showed with ample documentation that Freud's reconstruction of a real primal scene is ludicrous.

Let the reader, like the buyer, beware.

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PATRICK J. MAHONY, PH.D.
*Outremont, Que., Canada*

### Dr. Buckley Replies

SIR: Dr. Mahony notes, "I devoted some 40 pages to the patient's psychodynamics alone and some 50 to Freud's technique." The writer of a review article covering three of the major case histories does not have this commodious luxury. *Ipso facto*, one has to be highly selective about which aspects of the voluminous Freud literature receive attention. Dr. Mahony fails to recognize that in my review the emphasis was on the clinical issues in the case histories as they pertain to current practice and not on an exhaustive study of the historical scholarship on Freud and his patients nor on literary and linguistic exegesis. My examination was designed to highlight advances in psychodynamic theory and technique since Freud's time.

Dr. Mahony's warning to the reader is, of course, always true.

PETER BUCKLEY, M.B., CH.B.
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*Reprints of letters to the Editor are not available.*

### Corrections

In the review by Ralph Hoffman, M.D., of the book *Thought Without Language*, edited by L. Weiskrantz (March 1990 issue, pp. 365–366), the reference was inadvertently deleted. The reference should be

1. Wittgenstein L: Remarks on the Philosophy of Psychology, vol 2. Edited by von Wright GH, Nyman H. Chicago, University of Chicago Press, 1980, section 9

In the paper "Suicide and Schizophrenia: Data From a Prospective Community Study" by Lawrence J. Cohen, Ph.D., et al. (May 1990 issue, pp. 602–607), one of the instruments reported was mistakenly identified as the SCL-90-R. In fact, the Brief Symptom Inventory (Derogatis LR, Melisoratos N: The Brief Symptom Inventory: an introductory report. Psychol Med 1983; 13:595–605) was used.

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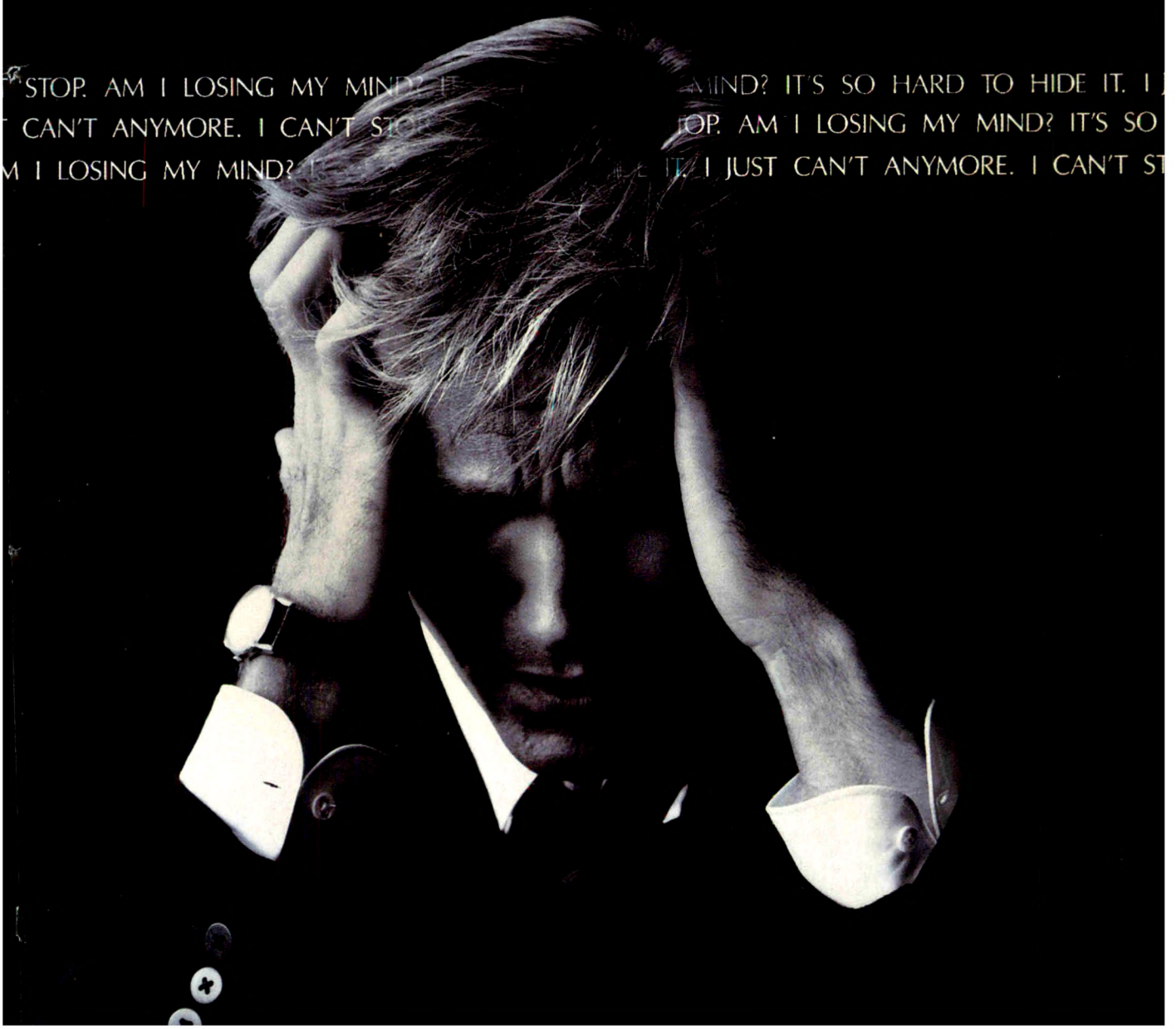

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**References: 1.** DeVeaugh-Geiss J, Landau P, Katz R. Treatment of obsessive-compulsive disorder with clomipramine. Psychiatr Ann. *1989;19:97-101.* **2.** Insel TR, Murphy DL, Cohen RM et al. Obsessive-compulsive disorder: A double-blind trial of clomipramine and clorgyline. Arch Gen Psychiatry. *1983;40:605-611.* **3.** Zohar J, Insel TR, Zohar-Kadouch RC et al. Serotonergic responsivity in obsessive-compulsive disorder. Arch Gen Psychiatry. *1988;45:167-171.* **4.** *Data on file, CIBA-GEIGY Corporation.*

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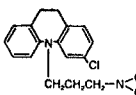
Anafranil, clomipramine hydrochloride, is an antiobsessional drug that belongs to the class (dibenzazepine) of pharmacologic agents known as tricyclic antidepressants. Anafranil is available as capsules of 25, 50, and 75 mg for oral administration.

Clomipramine hydrochloride is 3-chloro-5-[3-(dimethylamino)propyl]-10,11-dihydro-5H-dibenz[b,f]azepine monohydrochloride, and its structural formula is:




Clomipramine hydrochloride is a white to off-white crystalline powder. It is freely soluble in water, in methanol, and in methylene chloride, and insoluble in ethyl ether and in hexane. Its molecular weight is 351.3.

*Inactive Ingredients.* D&C Red No. 33 (25-mg capsules only), D&C Yellow No. 10, FD&C Blue No. 1 (50-mg capsules only), FD&C Yellow No. 6, gelatin, magnesium stearate, methylparaben, propylparaben, silicon dioxide, sodium lauryl sulfate, starch, and titanium dioxide.

### CLINICAL PHARMACOLOGY

**Pharmacodynamics**

Clomipramine (CMI) is presumed to influence obsessive and compulsive behaviors through its effects on serotonergic neuronal transmission. The actual neurochemical mechanism is unknown, but CMI's relatively selective capacity to inhibit the reuptake of serotonin (5-HT) as compared to norepinephrine (NE) may be important.

**Pharmacokinetics**

***Absorption/Bioavailability:*** CMI from Anafranil capsules is as bioavailable as CMI from a solution. The bioavailability of CMI from capsules is not significantly affected by food.

In a dose proportionality study involving multiple CMI doses, steady-state plasma concentrations ($C_{ss}$) and area-under-plasma-concentration-time curves (AUC) of CMI and CMI's major active metabolite, desmethylclomipramine (DMI), were not proportional to dose over the ranges evaluated, i.e., between 25-100 mg/day and between 25-150 mg/day, although $C_{ss}$ and AUC are approximately linearly related to dose between 100-150 mg/day. The relationship between dose and CMI/DMI concentrations at higher daily doses has not been systematically assessed, but if there is significant dose dependency at doses above 150 mg/day, there is the potential for dramatically higher $C_{ss}$ and AUC even for patients dosed within the recommended range. This may pose a potential risk to some patients (see WARNINGS and PRECAUTIONS, Drug Interactions).

After a single 50-mg oral dose, maximum plasma concentrations of CMI occur within 2-6 hours (mean, 4.7 hr) and range from 56 ng/ml to 154 ng/ml (mean, 92 ng/ml). After multiple daily doses of 150 mg of Anafranil, steady-state maximum plasma concentrations range from 94 ng/ml to 339 ng/ml (mean, 218 ng/ml) for CMI and from 134 ng/ml to 532 ng/ml (mean, 274 ng/ml) for DMI. No pharmacokinetic information is available for doses ranging from 150 mg/day to 250 mg/day, the maximum recommended daily dose.

***Distribution:*** CMI distributes into cerebrospinal fluid (CSF) and brain and into breast milk. DMI also distributes into CSF, with a mean CSF/plasma ratio of 2.6. The protein binding of CMI is approximately 97%, principally to albumin, and is independent of CMI concentration. The interaction between CMI and other highly protein-bound drugs has not been fully evaluated, but may be important (see PRECAUTIONS, Drug Interactions).

***Metabolism:*** CMI is extensively biotransformed to DMI and other metabolites and their glucuronide conjugates. DMI is pharmacologically active, but its effects on OCD behaviors are unknown. These metabolites are excreted in urine and feces, following biliary elimination. After a 25-mg radiolabeled dose of CMI in two subjects, 60% and 51%, respectively, of the dose were recovered in the urine and 32% and 24%, respectively, in feces. In the same study, the combined urinary recoveries of CMI and DMI were only about 0.8-1.3% of the dose administered. CMI does not induce drug-metabolizing enzymes, as measured by antipyrine half-life.

***Elimination:*** Evidence that the $C_{ss}$ and AUC for CMI and DMI may increase disproportionately with increasing oral doses suggests that the metabolism of CMI and DMI may be capacity limited. This fact must be considered in assessing the estimates of the pharmacokinetic parameters presented below, as these were obtained in individuals exposed to doses of 150 mg. If the pharmacokinetics of CMI and DMI are nonlinear at doses above 150 mg, their elimination half-lives may be considerably lengthened at doses near the upper end of the recommended dosing range (i.e., 200 mg/day to 250 mg/day). Consequently, CMI and DMI may accumulate, and this accumulation may increase the incidence of any dose- or plasma-concentration-dependent adverse reactions, in particular seizures (see WARNINGS).

After a 150-mg dose, the half-life of CMI ranges from 19 hours to 37 hours (mean, 32 hr) and that of DMI ranges from 54 hours to 77 hours (mean, 69 hr). Steady-state levels after multiple dosing are typically reached within 7-14 days for CMI. Plasma concentrations of the metabolite exceed the parent drug on multiple dosing. After multiple dosing with 150 mg/day, the accumulation factor for CMI is approximately 2.5 and for DMI is 4.6. Importantly, it may take two weeks or longer to achieve this extent of accumulation at constant dosing because of the relatively long elimination half-lives of CMI and DMI (see DOSAGE AND ADMINISTRATION). The effects of hepatic and renal impairment on the disposition of Anafranil have not been determined.

***Pharmacokinetic Interactions:*** Coadministration of haloperidol with CMI increases plasma concentrations of CMI. Coadministration of CMI with phenobarbital increases plasma concentrations of phenobarbital (see PRECAUTIONS, Drug Interactions). Younger subjects (18-40 years of age) tolerated CMI better and had significantly lower steady-state plasma concentrations, compared with subjects over 65 years of age. Children under 15 years of age had significantly lower plasma concentration/dose ratios, compared with adults. Plasma concentrations of CMI were significantly higher in smokers than in nonsmokers.

### INDICATIONS AND USAGE

Anafranil is indicated for the treatment of obsessions and compulsions in patients with Obsessive-Compulsive Disorder (OCD). The obsessions or compulsions must cause marked distress, be time-consuming, or significantly interfere with social or occupational functioning, in order to meet the DSM-III-R (circa 1989) diagnosis of OCD.

Obsessions are recurrent, persistent ideas, thoughts, images, or impulses that are ego-dystonic. Compulsions are repetitive, purposeful, and intentional behaviors performed in response to an obsession or in a stereotyped fashion, and are recognized by the person as excessive or unreasonable.

The effectiveness of Anafranil for the treatment of OCD was demonstrated in multicenter, placebo-controlled, parallel-group studies, including two 10-week studies in adults and one 8-week study in children and adolescents 10-17 years of age. Patients in all studies had moderate-to-severe OCD (DSM-III), with mean baseline ratings on the Yale-Brown Obsessive Compulsive Scale (YBOCS) ranging from 26 to 28 and a mean baseline rating of 10 on the NIMH Clinical Global Obsessive Compulsive Scale (NIMH-OC). Patients taking CMI experienced a mean reduction of approximately 10 on the YBOCS, representing an average improvement on this scale of 35% to 42% among adults and 37% among children and adolescents. CMI treated patients experienced a 3.5 unit decrement on the NIMH-OC. Patients on placebo showed no important clinical response on either scale. The maximum dose was 250 mg/day for most adults and 3 mg/kg/day (up to 200 mg) for all children and adolescents.

The effectiveness of Anafranil for long-term use (i.e., for more than 10 weeks) has not been systematically evaluated in placebo-controlled trials. The physician who elects to use Anafranil for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND

### CONTRAINDICATIONS

Anafranil is contraindicated in patients with a history of hypersensitivity to Anafranil or other tricyclic antidepressants.

Anafranil should not be given in combination, or within 14 days of treatment, with a monoamine oxidase (MAO) inhibitor. Hyperpyretic crisis, seizures, coma, and death have been reported in patients receiving such combinations.

Anafranil is contraindicated during the acute recovery period after a myocardial infarction.

### WARNINGS

**Seizures**

During premarket evaluation, seizure was identified as the most significant risk of Anafranil use.

The observed cumulative incidence of seizures among patients exposed to Anafranil at doses up to 300 mg/day was 0.64% at 90 days, 1.12% at 180 days, and 1.45% at 365 days. The cumulative rates cited correct the crude rate (i.e., 0.7%, 25/3519) for the variable duration of exposure times among the patients who participated in the development program.

Although dose appears to be a predictor of seizure, there is a confounding of dose and duration of exposure, making it difficult to assess independently the effect of either factor alone. The ability to predict the occurrence of seizures in subjects exposed to doses of CMI greater than 250 mg is limited, given that the plasma concentration of CMI may be dose-dependent and may vary among subjects given the same dose. Nevertheless, prescribers are advised to limit the daily dose to a maximum of 250 mg in adults and 3 mg/kg (or 200 mg) in children and adolescents (see DOSAGE AND ADMINISTRATION).

Rare reports of fatalities in association with seizures have been recorded by foreign post-marketing surveillance systems over the 20 years of Anafranil's nondomestic marketing. In some of these cases, Anafranil had been administered with other epileptogenic agents; in others, the patients involved had possibly predisposing medical conditions.

Caution should be used in administering Anafranil to patients with a history of seizures or other predisposing factors, e.g., brain damage of varying etiology, alcoholism, and concomitant use with other drugs that lower the seizure threshold.

Physicians should discuss with patients the risk of taking Anafranil while engaging in activities in which sudden loss of consciousness could result in serious injury to the patient or others, e.g., the operation of complex machinery, driving, swimming, climbing.

### PRECAUTIONS

**General**

***Suicide:*** Since depression is a commonly associated feature of OCD, the risk of suicide must be considered. Prescriptions for Anafranil should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

***Cardiovascular Effects:*** Modest orthostatic decreases in blood pressure and modest tachycardia were each seen in approximately 20% of patients taking Anafranil in clinical trials; but patients were frequently asymptomatic. Among approximately 1400 patients treated with CMI in the premarketing experience who had ECGs, 1.5% developed abnormalities during treatment, compared with 3.1% of patients receiving active control drugs and 0.7% of patients receiving placebo. The most common ECG changes were PVCs, ST-T wave changes, and intraventricular conduction abnormalities. These changes were rarely associated with significant clinical symptoms. Nevertheless, caution is necessary in treating patients with known cardiovascular disease, and gradual dose titration is recommended.

***Psychosis, Confusion, And Other Neuropsychiatric Phenomena:*** Patients treated with Anafranil have been reported to show a variety of neuropsychiatric signs and symptoms including delusions, hallucinations, psychotic episodes, confusion, and paranoia. Because of the uncontrolled nature of many of the studies, it is impossible to provide a precise estimate of the extent of risk imposed by treatment with Anafranil. As with tricyclic antidepressants to which it is closely related, Anafranil may precipitate an acute psychotic episode in patients with unrecognized schizophrenia.

***Mania/Hypomania:*** During premarketing testing of Anafranil in patients with affective disorder, hypomania or mania was precipitated in several patients. Activation of mania or hypomania has also been reported in a small proportion of patients with affective disorder treated with marketed tricyclic antidepressants, which are closely related to Anafranil.

***Hepatic Changes:*** During premarketing testing, Anafranil was occasionally associated with elevations in SGOT and SGPT (pooled incidence of approximately 1% and 3%, respectively) of potential clinical importance (i.e., values greater than 3 times the upper limit of normal). In the vast majority of instances these enzyme increases were not associated with other clinical findings suggestive of hepatic injury; moreover, none were jaundiced. Rare reports of more severe liver injury, some fatal, have been recorded in foreign post-marketing experience. Caution is indicated in treating patients with known liver disease, and periodic monitoring of hepatic enzyme levels is recommended in such patients.

***Hematologic Changes:*** Although no instances of severe hematologic toxicity were seen in the premarketing experience with Anafranil, there have been post-marketing reports of leukopenia, agranulocytosis, thrombocytopenia, anemia, and pancytopenia in association with Anafranil use. As is the case with tricyclic antidepressants to which Anafranil is closely related, leukocyte and differential blood counts should be obtained in patients who develop fever and sore throat during treatment with Anafranil.

***Central Nervous System:*** More than 30 cases of hyperthermia have been recorded by nondomestic post-marketing surveillance systems. Most cases occurred when Anafranil was used in combination with other drugs when Anafranil and a neuroleptic were used concomitantly, the cases were sometimes considered to be examples of a neuroleptic malignant syndrome.

***Sexual Dysfunction:*** The rate of sexual dysfunction in male patients with OCD who were treated with Anafranil in the premarketing experience was markedly increased compared with placebo controls (i.e., 42% experienced ejaculatory failure and 20% experienced impotence, compared with 2.0% and 2.6%, respectively, in the placebo group). Approximately 85% of males with sexual dysfunction chose to continue treatment.

***Weight Changes:*** In controlled studies of OCD, weight gain was reported in 18% of patients receiving Anafranil, compared with 1% of patients receiving placebo. In these studies, 28% of patients receiving Anafranil had a weight gain of at least 7% of their initial body weight, compared with 4% of patients receiving placebo. Several patients had weight gains in excess of 25% of their initial body weight. Conversely, 5% of patients receiving Anafranil and 1% receiving placebo had weight losses of at least 7% of their initial body weight.

***Electroconvulsive Therapy:*** As with closely related tricyclic antidepressants, concurrent administration of Anafranil with electroconvulsive therapy may increase the risks; such treatment should be limited to those patients for whom it is essential, since there is limited clinical experience.

***Surgery:*** Prior to elective surgery with general anesthetics, therapy with Anafranil should be discontinued for as long as is clinically feasible, and the anesthetist should be advised.

***Use in Concomitant Illness:*** As with closely related tricyclic antidepressants, Anafranil should be used with caution in the following:

1. Hyperthyroid patients or patients receiving thyroid medication, because of the possibility of cardiac toxicity.
2. Patients with increased intraocular pressure, a history of narrow-angle glaucoma, or urinary retention, because of the anticholinergic properties of the drug.
3. Patients with tumors of the adrenal medulla (e.g., pheochromocytoma, neuroblastoma) in whom the drug may provoke hypertensive crises.
4. Patients with significantly impaired renal function.

***Withdrawal Symptoms:*** A variety of withdrawal symptoms have been reported in association with abrupt discontinuation of Anafranil, including dizziness, nausea, vomiting, headache, malaise, sleep disturbance, hyperthermia, and irritability. In addition, such patients may experience a worsening of psychiatric status. While the withdrawal effects of Anafranil have not been systematically evaluated in controlled trials, they are well known with closely related tricyclic antidepressants, and it is recommended that the dosage be tapered gradually and the patient monitored carefully during discontinuation (see DRUG ABUSE AND DEPENDENCE).

**Information for Patients**

Physicians are advised to discuss the following issues with patients for whom

1. The risk of seizure (see WARNINGS).
2. The relatively high incidence of sexual dysfunction among males (see PRECAUTIONS, Sexual Dysfunction).
3. Since Anafranil may impair the mental and/or physical abilities required for the performance of complex tasks, and since Anafranil is associated with a risk of seizures, patients should be cautioned about the performance of complex and hazardous tasks (see WARNINGS).
4. Patients should be cautioned about using alcohol, barbiturates, or other CNS depressants concurrently, since Anafranil may exaggerate their response to these drugs.
5. Patients should notify their physician if they become pregnant or intend to become pregnant during therapy.
6. Patients should notify their physician if they are breast-feeding.

**Drug Interactions**

The risks of using Anafranil in combination with other drugs have not been systematically evaluated. Given the primary CNS effects of Anafranil, caution is advised in using it concomitantly with other CNS-active drugs (see PRECAUTIONS, Information for Patients). Anafranil should *not* be used with MAO inhibitors (see CONTRAINDICATIONS).

Close supervision and careful adjustment of dosage are required when Anafranil is administered with anticholinergic or sympathomimetic drugs.

Several tricyclic antidepressants have been reported to block the pharmacologic effects of guanethidine, clonidine, or similar agents, and such an effect may be anticipated with CMI because of its structural similarity to other tricyclic antidepressants.

The plasma concentration of CMI has been reported to be increased by the concomitant administration of haloperidol; plasma levels of several closely related tricyclic antidepressants have been reported to be increased by the concomitant administration of either methylphenidate, cimetidine, or fluoxetine and such an effect may be anticipated with CMI as well. Administration of CMI has been reported to increase the plasma levels of phenobarbital, if given concomitantly (see CLINICAL PHARMACOLOGY, Pharmacokinetic Interactions).

Because Anafranil is highly bound to serum protein, the administration of Anafranil to patients taking other drugs that are highly bound to protein (e.g., warfarin, digoxin) may cause an increase in plasma concentrations of these drugs, potentially resulting in adverse effects. Conversely, adverse effects may result from displacement of protein-bound Anafranil by other highly bound drugs (see CLINICAL PHARMACOLOGY, Distribution).

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

In a 2-year bioassay, no clear evidence of carcinogenicity was found in rats given doses 20 times the maximum daily human dose. Three out of 235 treated rats had a rare tumor (hemangioendothelioma); it is unknown if these neoplasms are compound related.

In reproduction studies, no effects on fertility were found in rats given doses approximately 5 times the maximum daily human dose.

**Pregnancy Category C**

No teratogenic effects were observed in studies performed in rats and mice at doses up to 20 times the maximum daily human dose. Slight nonspecific fetotoxic effects were seen in the offspring of pregnant mice given doses 10 times the maximum daily human dose. Slight nonspecific embryotoxicity was observed in rats given doses 5-10 times the maximum daily human dose.

There are no adequate or well-controlled studies in pregnant women. Withdrawal symptoms, including jitteriness, tremor, and seizures, have been reported in neonates whose mothers had taken Anafranil until delivery. Anafranil should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers**

Anafranil has been found in human milk. Because of the potential for adverse reactions, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Pediatric Use**

In a controlled clinical trial in children and adolescents (10-17 years of age), 46 outpatients received Anafranil for up to 8 weeks. In addition, 150 adolescent patients have received Anafranil in open-label protocols for periods of several months to several years. Of the 196 adolescents studied, 50 were 13 years of age or less and 146 were 14-17 years of age. While the adverse reaction profile in this age group (see ADVERSE REACTIONS) is similar to that in adults, it is unknown what, if any, effects long-term treatment with Anafranil may have on the growth and development of children.

The safety and effectiveness in children below the age of 10 have not been established. Therefore, specific recommendations cannot be made for the use of Anafranil in children under the age of 10.

**Use in Elderly**

Anafranil has not been systematically studied in older patients; but 152 patients at least 60 years of age participating in U.S. clinical trials received Anafranil for periods of several months to several years. No unusual age-related adverse events have been identified in this elderly population, but these data are insufficient to rule out possible age-related differences, particularly in elderly patients who have concomitant systemic illnesses or who are receiving other drugs concomitantly.

### ADVERSE REACTIONS

**Commonly Observed**

The most commonly observed adverse events associated with the use of Anafranil and not seen at an equivalent incidence among placebo-treated patients were gastrointestinal complaints, including dry mouth, constipation, nausea, dyspepsia, and anorexia; nervous system complaints, including somnolence, tremor, dizziness, nervousness, and myoclonus; genitourinary complaints, including changed libido, ejaculatory failure, impotence, and micturition disorder; and other miscellaneous complaints, including fatigue, sweating, increased appetite, weight gain, and visual changes.

**Leading to Discontinuation of Treatment**

Approximately 20% of 3616 patients who received Anafranil in U.S. premarketing clinical trials discontinued treatment because of an adverse event. Approximately one-half of the patients who discontinued (9% of the total) had multiple complaints, none of which could be classified as primary. Where a primary reason for discontinuation could be identified, most patients discontinued because of nervous system complaints (5.4%), primarily somnolence. The second-most-frequent reason for discontinuation was digestive system complaints (1.3%), primarily vomiting and nausea.

**Incidence in Controlled Clinical Trials**

The following table enumerates adverse events that occurred at an incidence of 1% or greater among patients with OCD who received Anafranil in adult or pediatric placebo-controlled clinical trials. The frequencies were obtained from pooled data of clinical trials involving either adults receiving Anafranil (N = 322), placebo (N = 319) or children treated with Anafranil (N = 46) or placebo (N = 44). The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice, in which patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, provide the physician with a basis for estimating the relative contribution of drug and nondrug factors to the incidence of side effects in the populations studied.

**Incidence of Treatment-Emergent Adverse Experience in Placebo-Controlled Clinical Trials**
(Percentage of Patients Reporting)

| | Adults | | Children and Adolescents | |
|---|---|---|---|---|
| Body System/ Adverse Event* | Anafranil (N=322) | Placebo (N=319) | Anafranil (N=46) | Pla (N |
| **Nervous System** | | | | |
| Somnolence | 54 | 16 | 46 | |
| Tremor | 54 | 2 | 33 | |
| Dizziness | 54 | 14 | 41 | |
| Headache | 52 | 41 | 28 | |

| Body System/ Adverse Event* | Adults: Anafranil (N=322) | Adults: Placebo (N=319) | Children and Adolescents: Anafranil (N=46) | Children and Adolescents: Placebo (N=44) |
|---|---|---|---|---|
| Libido change | 21 | 3 | — | — |
| Nervousness | 18 | 2 | 4 | 2 |
| Myoclonus | 13 | — | 2 | — |
| Increased appetite | 11 | 2 | — | 2 |
| Paresthesia | 9 | 3 | 2 | 2 |
| Memory impairment | 9 | 1 | 7 | 2 |
| Anxiety | 9 | 4 | 2 | — |
| Twitching | 7 | 1 | 4 | 5 |
| Impaired concentration | 5 | 2 | — | — |
| Depression | 5 | 1 | — | — |
| Hypertonia | 4 | 1 | 2 | — |
| Sleep disorder | 4 | — | 9 | 5 |
| Psychosomatic disorder | 3 | — | — | — |
| Yawning | 3 | — | — | — |
| Confusion | 3 | — | 2 | — |
| Speech disorder | 3 | — | — | — |
| Abnormal dreaming | 3 | — | — | 2 |
| Agitation | 3 | — | — | — |
| Migraine | 3 | — | — | — |
| Depersonalization | 2 | — | 2 | — |
| Irritability | 2 | 2 | 2 | — |
| Emotional lability | 2 | — | — | 2 |
| Panic reaction | 1 | — | 2 | — |
| Aggressive reaction | — | — | 2 | — |
| Paresis | — | — | 2 | — |
| **Skin and Appendages** | | | | |
| Increased sweating | 29 | 3 | 9 | — |
| Rash | 8 | 1 | 4 | 2 |
| Pruritus | 6 | — | 2 | 2 |
| Dermatitis | 2 | — | — | 2 |
| Acne | 2 | 2 | — | 5 |
| Dry skin | 2 | — | — | 5 |
| Urticaria | 1 | — | — | — |
| Abnormal skin odor | — | — | 2 | — |
| **Digestive System** | | | | |
| Dry mouth | 84 | 17 | 63 | 16 |
| Constipation | 47 | 11 | 22 | 9 |
| Nausea | 33 | 14 | 9 | 11 |
| Dyspepsia | 22 | 10 | 13 | 2 |
| Diarrhea | 13 | 9 | 7 | 5 |
| Anorexia | 12 | — | 22 | 2 |
| Abdominal pain | 11 | 9 | 13 | 16 |
| Vomiting | 7 | 2 | 7 | — |
| Flatulence | 6 | 3 | — | 2 |
| Tooth disorder | 5 | — | — | — |
| Gastrointestinal disorder | 2 | — | — | 2 |
| Dysphagia | 2 | — | — | — |
| Esophagitis | 1 | — | — | — |
| Eructation | — | — | 2 | 2 |
| Ulcerative stomatitis | — | — | 2 | — |
| **Body as a Whole** | | | | |
| Fatigue | 39 | 18 | 35 | 9 |
| Weight increase | 18 | 1 | 2 | — |
| Flushing | 8 | — | 7 | — |
| Hot flushes | 5 | — | 2 | — |
| Chest pain | 4 | 4 | 7 | — |
| Fever | 4 | — | 2 | 7 |
| Allergy | 3 | 3 | 7 | 5 |
| Pain | 3 | 2 | 4 | 2 |
| Local edema | 2 | 4 | — | — |
| Chills | 2 | 1 | — | — |
| Weight decrease | — | — | 7 | — |
| Otitis media | — | — | 4 | 5 |
| Asthenia | — | — | 2 | — |
| Halitosis | — | — | 2 | — |
| **Cardiovascular System** | | | | |
| Postural hypotension | 6 | — | 4 | — |
| Palpitation | 4 | 2 | 4 | — |
| Tachycardia | 4 | — | 2 | — |
| Syncope | — | — | 2 | — |
| **Respiratory System** | | | | |
| Pharyngitis | 14 | 9 | — | 5 |
| Rhinitis | 12 | 10 | 7 | 9 |
| Sinusitis | 6 | 4 | 2 | 5 |
| Coughing | 6 | 6 | 4 | 5 |
| Bronchospasm | 2 | — | 7 | 2 |
| Epistaxis | 2 | — | — | 2 |
| Dyspnea | — | — | 2 | — |
| Laryngitis | — | 1 | 2 | — |
| **Urogenital System** | | | | |
| **Male and Female Patients Combined** | | | | |
| Micturition disorder | 14 | 2 | 4 | 2 |
| Urinary tract infection | 6 | 1 | — | — |
| Micturition frequency | 5 | 3 | — | — |
| Urinary retention | 2 | — | 7 | — |
| Dysuria | 2 | 2 | — | — |
| Cystitis | 2 | — | — | — |
| **Female Patients Only** | (N = 182) | (N = 167) | (N = 10) | (N = 21) |
| Dysmenorrhea | 12 | 14 | 10 | 10 |
| Lactation (nonpuerperal) | 4 | — | — | — |
| Menstrual disorder | 4 | 2 | — | — |
| Vaginitis | 2 | — | — | — |
| Leukorrhea | 2 | — | — | — |
| Breast enlargement | 2 | — | — | — |
| Breast pain | 1 | — | — | — |
| Amenorrhea | 1 | — | — | — |
| **Male Patients Only** | (N = 140) | (N = 152) | (N = 36) | (N = 23) |
| Ejaculation failure | 42 | 2 | 6 | — |
| Impotence | 20 | 3 | — | — |
| **Special Senses** | | | | |
| Abnormal vision | 18 | 4 | 7 | 2 |
| Taste perversion | 8 | — | 4 | — |
| Tinnitus | 6 | — | 4 | — |
| Abnormal lacrimation | 3 | 2 | — | — |
| Mydriasis | 2 | — | — | — |
| Conjunctivitis | 1 | — | — | — |
| Anisocoria | — | — | 2 | — |
| Blepharospasm | — | — | 2 | — |
| Ocular allergy | — | — | 2 | — |
| Vestibular disorder | — | — | 2 | 2 |
| **Musculoskeletal** | | | | |
| Myalgia | 13 | 9 | — | — |
| Back pain | 6 | 6 | — | — |
| Arthralgia | 3 | 5 | — | — |
| Muscle weakness | 1 | — | 2 | — |
| **Hemic and Lymphatic** | | | | |
| Purpura | 3 | — | — | — |
| Anemia | — | — | 2 | 2 |
| **Metabolic and Nutritional** | | | | |
| Thirst | 2 | 2 | — | 2 |

**Other Events Observed During the Premarketing Evaluation of Anafranil**

During clinical testing in the U.S., multiple doses of Anafranil were administered to approximately 3600 subjects. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, a modified World Health Organization dictionary of terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the 3525 individuals exposed to Anafranil who experienced an event of the type cited on at least one occasion while receiving Anafranil. All events are included except those already listed in the previous table, those reported in terms so general as to be uninformative, and those in which an association with the drug was remote. It is important to emphasize that although the events reported occurred during treatment with Anafranil, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in less than 1/1000 patients.

***Body as a Whole: Infrequent*** — general edema, increased susceptibility to infection, malaise. ***Rare*** — dependent edema, withdrawal syndrome.

***Cardiovascular System: Infrequent*** — abnormal ECG, arrhythmia, bradycardia, cardiac arrest, extrasystoles, pallor. ***Rare*** — aneurysm, atrial flutter, bundle branch block, cardiac failure, cerebral hemorrhage, heart block, myocardial infarction, myocardial ischemia, peripheral ischemia, thrombophlebitis, vasospasm, ventricular tachycardia.

***Digestive System: Infrequent*** — abnormal hepatic function, blood in stool, colitis, duodenitis, gastric ulcer, gastritis, gastroesophageal reflux, gingivitis, glossitis, hemorrhoids, hepatitis, increased saliva, irritable bowel syndrome, peptic ulcer, rectal hemorrhage, tongue ulceration, tooth caries. ***Rare*** — cheilitis, chronic enteritis, discolored feces, gastric dilatation, gingival bleeding, hiccup, intestinal obstruction, oral/pharyngeal edema, paralytic ileus, salivary gland enlargement.

***Endocrine System: Infrequent*** — hypothyroidism. ***Rare*** — goiter, gynecomastia, hyperthyroidism.

***Hemic and Lymphatic System: Infrequent*** — lymphadenopathy. ***Rare*** — leukemoid reaction, lymphoma-like disorder, marrow depression.

***Metabolic and Nutritional Disorder: Infrequent*** — dehydration, diabetes mellitus, gout, hypercholesterolemia, hyperglycemia, hyperuricemia, hypokalemia. ***Rare*** — fat intolerance, glycosuria.

***Musculoskeletal System: Infrequent*** — arthrosis. ***Rare*** — dystonia, exostosis, lupus erythematosus rash, bruising, myopathy, myositis, polyarteritis nodosa, torticollis.

***Nervous System: Frequent*** — abnormal thinking, vertigo. ***Infrequent*** — abnormal coordination, abnormal EEG, abnormal gait, apathy, ataxia, coma, convulsions, delirium, delusion, dyskinesia, dysphonia, encephalopathy, euphoria, extrapyramidal disorder, hallucinations, hostility, hyperkinesia, hypnagogic hallucinations, hypokinesia, leg cramps, manic reaction, neuralgia, paranoia, phobic disorder, psychosis, sensory disturbance, somnambulism, stimulation, suicidal ideation, suicide attempt, teeth-grinding. ***Rare*** — anticholinergic syndrome, aphasia, apraxia, catalepsy, cholinergic syndrome, choreoathetosis, generalized spasm, hemiparesis, hyperesthesia, hyperreflexia, hypoesthesia, illusion, impaired impulse control, indecisiveness, mutism, neuropathy, nystagmus, oculogyric crisis, oculomotor nerve paralysis, schizophrenic reaction, stupor, suicide.

***Respiratory System: Infrequent*** — bronchitis, hyperventilation, increased sputum, pneumonia. ***Rare*** — cyanosis, hemoptysis, hypoventilation, laryngismus.

***Skin and Appendages: Infrequent*** — alopecia, cellulitis, cyst, eczema, erythematous rash, genital pruritus, maculopapular rash, photosensitivity reaction, psoriasis, pustular rash, skin discoloration. ***Rare*** — chloasma, folliculitis, hypertrichosis, piloerection, seborrhea, skin hypertrophy, skin ulceration.

***Special Senses: Infrequent*** — abnormal accommodation, deafness, diplopia, earache, eye pain, foreign body sensation, hyperacusis, parosmia, photophobia, scleritis, taste loss. ***Rare*** — blepharitis, chromatopsia, conjunctival hemorrhage, exophthalmos, glaucoma, keratitis, labyrinth disorder, night blindness, retinal disorder, strabismus, visual field defect.

***Urogenital System: Infrequent*** — endometriosis, epididymitis, hematuria, nocturia, oliguria, ovarian cyst, perineal pain, polyuria, prostatic disorder, renal calculus, renal pain, testis disorder, urethral disorder, urinary incontinence, uterine hemorrhage, vaginal hemorrhage. ***Rare*** — albuminuria, anorgasmy, breast engorgement, breast fibroadenosis, cervical dysplasia, endometrial hyperplasia, premature ejaculation, pyelonephritis, pyuria, renal cyst, uterine inflammation, vulvar disorder.

## DRUG ABUSE AND DEPENDENCE

Anafranil has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. While a variety of withdrawal symptoms have been described in association with Anafranil discontinuation (see PRECAUTIONS, Withdrawal Symptoms), there is no evidence for drug-seeking behavior, except for a single report of potential Anafranil abuse by a patient with a history of dependence on codeine, benzodiazepines, and multiple psychoactive drugs. The patient received Anafranil for depression and panic attacks and appeared to become dependent after hospital discharge.

Despite the lack of evidence suggesting an abuse liability for Anafranil in foreign marketing, it is not possible to predict the extent to which Anafranil might be misused or abused once marketed in the U.S. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely.

## OVERDOSAGE

### Human Experience

In U.S. clinical trials, 2 deaths occurred in 12 reported cases of acute overdosage with Anafranil either alone or in combination with other drugs. One death involved a patient suspected of ingesting a dose of 7000 mg. The second death involved a patient suspected of ingesting a dose of 5750 mg. The 10 nonfatal cases involved doses of up to 5000 mg, accompanied by plasma levels of up to 1010 ng/mL. All 10 patients completely recovered. Among reports from other countries of Anafranil overdose, the lowest dose associated with a fatality was 750 mg. Based upon post-marketing reports in the United Kingdom, CMI's lethality in overdose is considered to be similar to that reported for closely related tricyclic compounds marketed as antidepressants.

### Signs and Symptoms

Signs and symptoms vary in severity depending upon factors such as the amount of drug absorbed, the age of the patient, and the time elapsed since drug ingestion. Blood and urine levels of Anafranil may not reflect the severity of poisoning: they have chiefly a qualitative rather than quantitative value, and they are unreliable indicators in the clinical management of the patient. The first signs and symptoms of poisoning with tricyclic antidepressants are generally severe anticholinergic reactions. CNS abnormalities may include drowsiness, stupor, coma, ataxia, restlessness, agitation, delirium, severe perspiration, hyperactive reflexes, muscle rigidity, athetoid and choreiform movements, and convulsions. Cardiac abnormalities may include arrhythmia, tachycardia, ECG evidence of impaired conduction, and signs of congestive heart failure, and in very rare cases, cardiac arrest. Respiratory depression, cyanosis, hypotension, shock, vomiting, hyperpyrexia, mydriasis, oliguria or anuria, and diaphoresis may also be present.

### Treatment

The recommended treatment for tricyclic overdose may change periodically. Therefore, it is recommended that the physician contact a poison control center for current information on treatment.

Because CNS involvement, respiratory depression, and cardiac arrhythmia can occur suddenly, hospitalization and close observation are necessary, even when the amount ingested is thought to be small or the initial degree of intoxication appears slight or moderate. All patients with ECG abnormalities should have continuous cardiac monitoring for at least 72 hours and be closely observed until well after the cardiac status has returned to normal; relapses may occur after apparent recovery. The slow intravenous administration of physostigmine salicylate has been reported to reverse the cardiovascular and CNS anticholinergic manifestations of tricyclic overdosage; however, it should not be used routinely, since it may induce seizures and cholinergic crises and there is persisting debate about its net utility.

In the alert patient, the stomach should be emptied promptly by induced emesis followed by lavage. In the obtunded patient, the airway should be secured with a cuffed endotracheal tube before beginning lavage (do not induce emesis). Lavage should be continued for 24 hours or longer, depending on the apparent severity of intoxication. Normal or half-normal saline should be used to avoid water intoxication, especially in children. Instillation of activated charcoal slurry may help reduce absorption of CMI.

External stimulation should be minimized to reduce the tendency for convulsions, and anticonvulsants may be necessary. If MAO inhibitors have been taken recently, barbiturates should not be used. Adequate respiratory exchange should be maintained, including intubation and artificial respiration, if necessary. Respiratory stimulants should not be used.

In severe hypotension or shock, the patient should be placed in an appropriate position and given a plasma expander, dopamine, or dobutamine by intravenous drip. The use of corticosteroids in shock is controversial and may be contraindicated in cases of overdosage with tricyclic antidepressants. Digitalis may increase conduction abnormalities and further irritate an already sensitized myocardium. If congestive heart failure necessitates rapid digitalization, particular care must be exercised. Hyperpyrexia should be controlled by whatever external means are available, including ice packs and cooling sponge baths, if necessary. Hemodialysis, peritoneal dialysis, exchange transfusions, and forced diuresis have generally been reported as ineffective because of the rapid fixation of Anafranil in tissues.

## DOSAGE AND ADMINISTRATION

The treatment regimens described below are based on those used in controlled clinical trials of Anafranil in 520 adults, and 91 children and adolescents with OCD. During initial titration, Anafranil should be given in divided doses with meals to reduce gastrointestinal side effects. The goal of this initial titration phase is to minimize side effects by permitting tolerance to side effects to develop or allowing the patient time to adapt if tolerance does not develop.

Because both CMI and its active metabolite, DMI, have long elimination half-lives, the prescriber should take into consideration the fact that steady-state plasma levels may not be achieved until 2-3 weeks after dosage change (see CLINICAL PHARMACOLOGY). Therefore, after initial titration, it may be appropriate to wait 2-3 weeks between further dosage adjustments.

### Initial Treatment/Dose Adjustment (Adults)

Treatment with Anafranil should be initiated at a dosage of 25 mg daily and gradually increased, as tolerated, to approximately 100 mg during the first 2 weeks. During initial titration, Anafranil should be given in divided doses with meals to reduce gastrointestinal side effects. Thereafter, the dosage may be increased gradually over the next several weeks, up to a maximum of 250 mg daily. After titration, the total daily dose may be given once daily at bedtime to minimize daytime sedation.

### Initial Treatment/Dose Adjustment (Children and Adolescents)

As with adults, the starting dose is 25 mg daily and should be gradually increased (also given in divided doses with meals to reduce gastrointestinal side effects) during the first 2 weeks, as tolerated, up to a daily maximum of 3 mg/kg or 100 mg, whichever is smaller. Thereafter, the dosage may be increased gradually over the next several weeks up to a daily maximum of 3 mg/kg or 200 mg, whichever is smaller (see PRECAUTIONS, Pediatric Use). As with adults, after titration, the total daily dose may be given once daily at bedtime to minimize daytime sedation.

### Maintenance/Continuation Treatment (Adults, Children, and Adolescents)

While there are no systematic studies that answer the question of how long to continue Anafranil, OCD is a chronic condition and it is reasonable to consider continuation for a responding patient. Although the efficacy of Anafranil after 10 weeks has not been documented in controlled trials, patients have been continued in therapy under double-blind conditions for up to 1 year without loss of benefit. However, dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for treatment. During maintenance, the total daily dose may be given once daily at bedtime.

## HOW SUPPLIED

*Capsules 25 mg* — ivory/melon yellow (imprinted ANAFRANIL 25 mg)
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Unit Dose (blister pack)
Box of 100 (strips of 10) ..... NDC 0083-0115-32
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Bottles of 100 ..... NDC 0083-0117-30
Unit Dose (blister pack)
Box of 100 (strips of 10) ..... NDC 0083-0117-32

Do not store above 86°F (30°C). Protect from moisture.

*Dispense in tight container (USP).*

## ANIMAL TOXICOLOGY

Testicular and lung changes commonly associated with tricyclic compounds have been observed with Anafranil. In 1- and 2-year studies in rats, changes in the testes (atrophy, aspermatogenesis, and calcification) and drug-induced phospholipidosis in the lungs were observed at doses 4 times the maximum daily human dose. Testicular atrophy was also observed in a 1-year oral toxicity study in dogs at 10 times the maximum daily human dose.

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In addition, authors must obtain letters of permission from publishers for use of extensive quotations (more than 500 words). The *Journal* does not publish tables or figures that have been previously published or submitted elsewhere.

### Disclosure of Commercial Interests

All forms of support, including drug company support, must be acknowledged in the author's footnote (see "Acknowledgments" under the Title Page section). Also, authors must disclose in their cover letter any commercial or financial involvements that might present an appearance of a conflict of interest in connection with the submitted article, including but not limited to institutional or corporate affiliations not already specified in the author's footnote, paid consultancies, stock ownership or other equity interests, and patent ownership. At the Editor's discretion, this information may be shared with reviewers. Such involvements will not be grounds for automatic rejection of the manuscript. Should the article be accepted for publication, the Editor and the authors will consult on whether, and to what extent, this information should be included in the published article.

### Patient Anonymity

Ethical as well as legal considerations require careful attention to the protection of a patient's anonymity in case reports and elsewhere. Identifying information such as names, initials, hospital numbers, and dates must be avoided. In addition, authors should disguise identifying information when discussing the characteristics and personal history of patients.

### Informed Consent

Manuscripts that report the results of experimental investigation with human subjects must include a statement that informed consent was obtained after the procedure(s) had been fully explained. In the case of children, authors are asked to include information about whether the child's assent was obtained.

### Review Process

All papers are reviewed to determine the originality, validity, and importance of content and conclusions. In addition to the regular review process, peer review for statistical content may be required for some manuscripts. This will be determined by the *Journal*'s Statistical Editors. Authors will be sent reviewer comments that are judged to be useful to them. All reviewers remain anonymous. Once the Editor has made a final decision on a paper, the authors of that paper will be informed.

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The original manuscript and four copies should be submitted to John C. Nemiah, M.D., Editor, *American Journal of Psychiatry*, 1400 K St., N.W., Washington, DC 20005. All correspondence will be sent to the first-named author unless otherwise specified. Papers should be accompanied by a cover letter indicating that the paper is intended for publication and specifying for which section of the *Journal* it is being submitted (i.e., Special Article, Regular Article, or Clinical and Research Report); papers will only be reviewed after such a statement has been received from the author.

Authors will be notified of the receipt of their paper and

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Single case reports except for detailed longitudinal studies should be submitted as Letters to the Editor. All single case reports will be peer reviewed. Reports of successfully treated patients must include data on the number of patients treated unsuccessfully by the same method, with an indication of the temporal order of the successes and failures.

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Authors may submit their papers before the annual meeting, but such papers cannot be published until after the meeting. All papers must be accompanied by a statement that they are in final form. These papers are subject to the same peer review as other papers and must conform to the requirements for one of the types of articles specified in the next section.

## TYPES OF ARTICLES

### Special Articles

These are usually overview articles that bring together important information on a topic of general interest to psychiatry. Authors who have ideas for such articles are advised to check with the Editorial Office to ensure that a similar work has not already been submitted. Special Articles may not exceed 7,500 words (no more than 25 double-spaced pages—including an abstract of no more than 100 words, tables, and figures) and may not include more than 100 references.

### Regular Articles

Regular Articles are original communications of scientific excellence in psychiatric medicine and advances in clinical research. Regular Articles contain no more than 3,800 words, including an abstract of no more than 100 words, references, tables, and figures. A table or figure that fills one-half of a vertical manuscript page equals 100 words of text; one that fills one-half of a horizontal page equals 150 words. Articles that exceed 3,800 words will be returned unreviewed to the authors.

### Clinical and Research Reports

Clinical and Research Reports may contain no more than one table and a maximum of 10 references; figures may not be used. Papers may contain a **maximum** of 1,300 words, including an abstract of no more than 40 words, references, and an optional table (estimate 15 words per reference, 100 words for a double-spaced table that fills one-half of a vertical page, and 150 words for a double-spaced table that fills one-half of a horizontal page). These articles present 1) new research findings, 2) data from pilot studies, 3) worthwhile replication studies, and 4) clinical studies involving a number of patients. Essays, program descriptions, literature reviews, and single case reports do not meet the criteria for this section. Submissions that exceed 1,300 words or contain figures will be returned to the author.

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All parts of the manuscript, including case reports, quotations, references, and tables, must be **double-spaced** throughout. Manuscripts must be typed in upper- and lowercase on one side only of 8½×11 inch **nonerasable** bond paper. All four margins must be 1½ inches. The manuscript should be arranged in the following order, with each item beginning a new page: 1) title page, 2) abstract, 3) text, 4) references, and 5) tables and/or figures. All pages must be numbered.

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**Title.** The title should be informative and as brief as possible. Two-part titles should be avoided.

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### Abstract

The abstract is a single paragraph no longer than 100 words for Special Articles and Regular Articles and no longer than 40 words for Clinical and Research Reports.

### Text

Authors should use the active voice and first person; headings and subheadings should be inserted at reasonable intervals. Footnotes to text may not be used, and summaries are usually unnecessary.

**Research design and statistics.** The following information regarding research design should be included: 1) a clearly stated hypothesis, 2) the names of the statistical tests used, 3) whether tests were one- or two-tailed, and 4) what test was used for each set of data. Reporting of standard deviations, rather than standard errors of the mean, is required. Statistical tests that are not well known should be referenced. **All** significant and important nonsignificant results must include the test value, degree(s) of freedom, and probability. For example, "The analysis of variance indicated that those who abstained from coffee had significantly higher course grades than those who did not abstain ($F=4.32$, $df=3, 17$, $p< 0.05$)." Reviewers will evaluate the appropriateness of the analyses.

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References are numbered and listed by their order of appearance in text; the text citation is followed by the appropriate reference number in parentheses. Do not arrange the list alphabetically. References in tables and figures are numbered as though the tables and figures were part of the text.

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Type references in the style shown below, **double-spaced throughout.** List up to three authors; designate one or more authors past the third as "et al." Abbreviations of journal names should conform to the style used in *Index Medicus*; journals not indexed there should not be abbreviated.

1. Noyes R Jr, DuPont RL Jr, Pecknold JC, et al: Alprazolam in panic disorder and agoraphobia, results from a multicenter trial, II: patient acceptance, side effects, and safety. Arch Gen Psychiatry 1988; 45:423–428
2. Kaplan HI, Sadock BJ (eds): Comprehensive Textbook of Psychiatry, 4th ed, vol 2. Baltimore, Williams & Wilkins, 1985
3. Fyer AJ, Manuzza S, Endicott J: Differential diagnosis and assessments of anxiety: recent developments, in Psychopharmacology: The Third Generation of Progress. Edited by Meltzer HY. New York, Raven Press, 1987

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### Figures

Figures are considered as text and are subject to revision by the authors upon recommendation of the Editors. Figures should, however, be professionally prepared. Glossy or other camera-ready prints should accompany the submitted manuscript. Computer-generated figures that do not meet quality printing standards will be returned for revision. The first author's name, the title of the paper, the figure number, and the top of the figure should be noted on a label affixed to the back of each figure. All figure titles and footnotes should be typed and sent together on a separate page.

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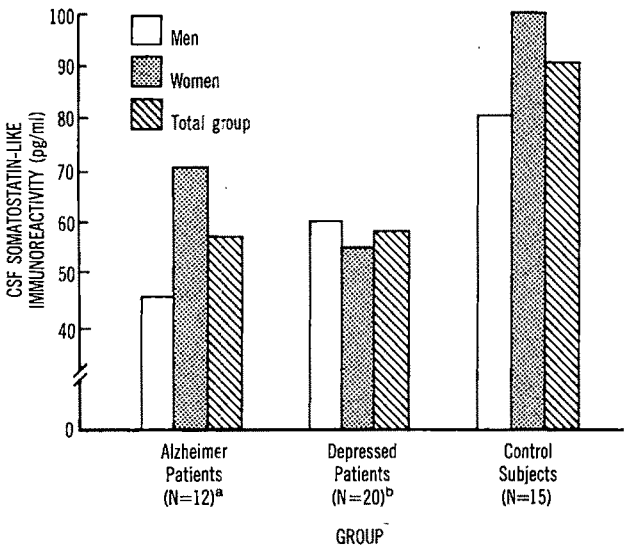
**FIGURE 1. Mean CSF Somatostatin Levels of Patients With Alzheimer's Disease, Older Depressed Patients, and Age-Matched Control Subjects**




[a]Significant difference between men and women ($t=1.81$, $df=10$, $p<0.05$) and between the total Alzheimer's disease group and the total control group ($t=2.49$, $df=25$, $p<0.01$).
[b]Significant difference between the total depressed group and the total control group ($t=2.75$, $df=33$, $p<0.005$).

cient, headings may be placed diagonally on the axis. Main headings should consist of upper-case letters only, subheadings of upper- and lower-case, and other type (e.g., keys, flow chart segments) of lower-case with only an initial upper-case letter. All parenthetical material should be lower-case. Do not use idiosyncratic abbreviations.

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1. Do not use solid black shading; rather, include outlined white among shadings.
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3. Error bars should not be used.
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5. The vertical axis should generally begin at zero; to save space, a double slash may take the place of an unused portion of the vertical axis.
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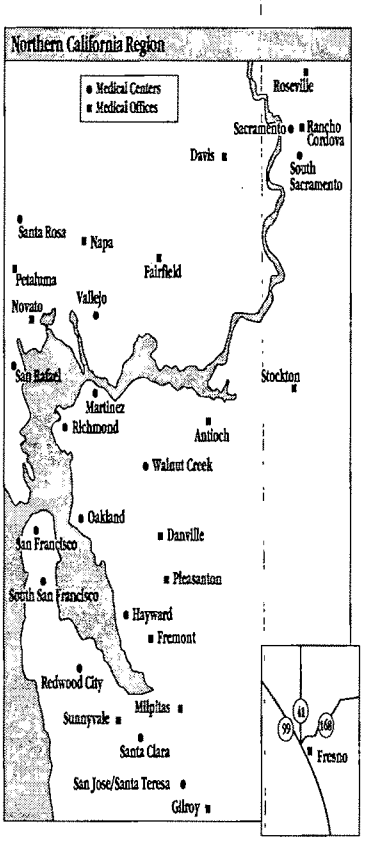


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In affiliation with
Capital District Psychiatric Center
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Seeking a Chairperson and Chief of Service for the Department of Psychiatry of an Academic Health Sciences Center. The scope of responsibilities include Administration, Patient Care, Research and Education. Qualified candidates may send a Curriculum Vitae and references to:

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Chairperson of Psychiatry Search Committee
Albany Medical Center, A-74
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Falmouth is not only a resort community, with beaches and boating, but also has a strong year-round flavor, with the world-renowned Woods Hole Oceanographic Institute and Marine Biological Laboratories, and many other marine science-related institutions. After school activities and leisure are abundant, offering the resources of a community full of accomplished artists, musicians, writers and intellectuals in various fields. The school system is excellent; the setting is beautiful.

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If you are interested, please send a C.V. to Mr. Alexander Ziss, Vice President for Clinical Services, Falmouth Hospital, Falmouth, MA 02540.

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## AUGUST 1990

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